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## NEUROLOGIC DISEASES

*Special Editor*

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## INTRODUCTION TO SYMPOSIUM ON NEUROLOGIC DISEASES

THE character of the clinical material on the neurologic wards of a general hospital has changed greatly in the last 25 years. The introduction of effective antimicrobial agents has almost entirely eliminated dementia paralytica, tabes dorsalis, and other late manifestations of syphilis in the nervous system, and the bacterial meningitides are no longer a great therapeutic problem. Combined system disease and diseases of the nervous system secondary to nutritional deficiency are now clinical rarities.

The efforts of the neurologists are now directed toward the solution of the problems presented by the metabolic and degenerative diseases of the nervous system. Significant advances have been made in the understanding of the pathogenesis of a number of these diseases, and effective forms of therapy have been introduced. Attention is also being paid to the study of the incidence, geographic distribution, and role of hereditary factors in diseases of the nervous system.

The Editors of the JOURNAL have thought it advisable to devote this issue to a presentation of the status of a number of these diseases. It has not been possible to include all the common ones, but an attempt has been made to select those which are subject to active investigation. It is hoped that this will bring the readers up to date with regard to these important diseases and also give them a broad view of the activities of the neurologist.

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# DESCRIPTIVE EPIDEMIOLOGY OF SELECTED NEUROLOGIC AND MYOPATHIC DISORDERS WITH PARTICULAR REFERENCE TO A SURVEY IN ROCHESTER, MINNESOTA

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## INTRODUCTION

RELIABLE data on the prevalence, geographic distribution, and population selectivity or differential incidence are available for only a few of the chronic neurologic and myopathic disorders. The purpose of this report is to compile such statistics from a number of selected sources, particularly those surveyed by the author and his associates, to discuss their potential usefulness and, in doing so, to point out the need for further descriptive and definitive epidemiologic or other investigations.

Most of the material analyzed in this report has come from the following sources:

1. Mortality statistics, including the underlying and contributory causes of deaths for 1951 for Canada and the underlying causes of deaths for several recent years in the United States and other countries.

2. Morbidity survey data, principally for multiple sclerosis, from several communities in the United States and Canada.

3. A detailed study of the frequency of selected diseases in the resident population of Rochester, Minnesota, based, for the most part, on the records of the Mayo Clinic. A description of methods is presented elsewhere.[1]

This report will deal almost exclusively with statistics obtained from sources which are believed to be reasonably representative of specified populations. Clinical impressions and relative hospital admission rates, with their inherent biases, have been adequately reviewed in the statistical discussions of standard neurology texts, and most of them will be avoided here.

## SURVEY PROCEDURES, DEFINITIONS, AND RATES

A satisfactory field study of a particular ailment calls for the clear identification of each affected person in the specified population. The need for precise clinical definitions and procedures for analyzing and presenting medical statistics has been reviewed in the excellent article by Dorn.[2]

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In general, standard clinical definitions were adopted for the diseases and syndromes enumerated in the surveys with which this author has been associated. However, for comparisons of mortality statistics and for use in many of the morbidity surveys, it has been necessary to adopt as the standard for a "case" a patient in the community for whom the examining physician made an appropriate diagnosis and in whom no later clinical report disputed such a diagnosis.

Many of the neurologic disorders have such a low incidence that case findings through individual examinations of the population are impractical; therefore one must resort to surveys of official reports (including death certificates) and surveys of recognized sources of medical information in the community, such as hospital or clinic records, and physicians' notes. The possible inadequacies of these sources include: failure of the patient to seek medical care, especially if his illness is mild or recent; failure of the physician to record or recall the patients he has observed; inaccuracies of diagnosis; and variations of the individual physicians in their clinical definitions of a disease or syndrome.

The Rochester, Minnesota, data, because of the unusual opportunities for complete case collection, avoid some of these problems; however, the small population in the community (30,000) means that the rates obtained are subject to appreciable chance fluctuation effect. However, since they are the only population survey data available for many of the conditions covered in this report, they are being presented in some detail.

Since a major reason for these statistical studies is to obtain data for comparisons with other populations, a word of caution is necessary in the use of such statistics. One cannot always accept as significant, with regard to the natural history of disease, small differences in community incidence rates (even if the differences are greater than would result by statistical chance alone and even where medical practice and survey procedures in the communities appear to be similar.) In the multiple sclerosis studies described later, prevalence rates between some communities differed to such a large degree that it is reasonably sure that the geographic correlation is a real one and that its explanation will clarify the cause of multiple sclerosis.

Comparisons of the frequency of illnesses in different populations require the use of suitable rates. To obtain rates one must know the size of the population "at risk" (denominator) as well as the number affected (numerator) for a stated period of time. The selection of a particular rate depends upon the clinical characteristics of the disease under study, the source of information, the delineation of the population "at risk," and the point which the investigator is trying to present or stress.

Some available frequency data have been misleading because they fail to distinguish between incidence and prevalence. An incidence rate, i.e., the number of newly developed (or newly discovered) cases per unit of population during a stated period of time, is preferred for conditions which are acute and of short duration; a prevalence rate, or the number of cases per unit of population at some specific moment (or, realistically, on a specified day), is more often preferred for disorders with an insidious onset and a long (many years) average duration. Given the same rates of incidence, a disease with a long duration will be found to be more prevalent than one of shorter durations.

When it is practical, both incidence and prevalence rates will be presented, for each has some particular advantage in describing the impact of the disease on the population. The incidence rates for each of several years may show a trend or a fluctuation with time which reflects the behavior of some causative factor. However, for a disease with an insidious onset, annual incidence rates based on survey data are likely to be inaccurate or incomplete. Prevalence rates, in which the patients living on a specified date are counted with respect to the total population on that date, are the most convenient rates to obtain in the course of a population survey for a chronic disease. Prevalence rates, however, reflect the annual incidence rates and the average duration of the illness in the community, but they are also affected by migration of patients and others into and out of the community.

In most epidemiologic studies, one selects the rate which can best illustrate the closest association of the affected to the specific population "at risk." For example, myelodysplasia could be measured in terms of incidence or prevalence among the total population but is best presented, for comparative studies, as a birth incidence rate; i.e., the ratio of newborn affected infants to the total number of births over a specific time. This type of rate is influenced less by circumstances which might be unrelated to the myelodysplasia than is a rate based on the number of cases in the population of all ages, since the latter would be affected by the age distribution of the population and the fertility rate as well as by direct factors responsible for myelodysplasia.

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## THE INTERRELATIONSHIP OF GENETICS AND EPIDEMIOLOGY

In the epidemiologic consideration of disease, environmental factors are usually stressed, and often only little consideration is given to the host factor, which is more or less synonymous with "heredity" or "constitutional predisposition." Knowledge of the role of heredity in the causation of disease, however, has lately advanced so rapidly that no serious-minded physician or epidemiologist can afford to ignore it. The relationship of genetics and epidemiology is exceedingly close; the modern geneticist operates at the population level, thinks in terms of a dynamic balance between mutation and selection, and uses the same tools as those of the epidemiologist.

The interplay of complex situations and environments on the genetic background of the individual in time determines the presence of disease, so that it has become more and more difficult to differentiate between a genetic and a "nongenetic" disease. When disorders are observed in familial aggregations, it is desirable to clarify the relative roles of heredity and common exposure to some environmental stress. Even where a hereditary factor is deemed critical, environmental conditions may affect the time of onset of the disease, the rapidity of its progression, and perhaps the development of new mutations which may alter the composition of the gene pool of the population. Prevention and ultimate control of diseases of "exogenous" origin require removal or alteration of the agent, alteration of the environment, or some immunologic or biochemical change in the host; prevention and ultimate control of many genetic diseases await biochemical elucidation.

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## EVALUATING DISEASE FREQUENCY IN GENETIC AND EPIDEMIOLOGIC SURVEYS OF SMALL POPULATIONS

Hereditary diseases can be studied epidemiologically in two kinds of populations: (1) in small population groups or "isolates" in which these diseases appear to disseminate in a nonrandom fashion, and (2) in "mendelian" populations, i.e., collections of individuals who share a common gene pool, among whom random matings occur, and who, according to the Hardy-Weinberg law, are in equilibrium with respect to a pair of genes responsible for a disease. The incidence and prevalence of a genetic disease in a mendelian population would depend on the on the gene frequency in that population.

In keeping with the classic epidemiologic approach, it is desirable to know the extent and distribution of the disease in the population. An estimate of incidence based on the survey of an isolate may give a distorted picture, particularly when the isolate is descended from a single family or a small group of families in which one of the key progenitors had a genetic defect. This situation is illustrated by the high incidence of a dominant form of progressive muscular atrophy in the Salt Lake City area,[3] and it has been hypothesized that a similar situation about 250 years ago accounted for the present high incidence of amyotrophic lateral sclerosis among the Chamorro population of the Mariana Islands.[4] Factors of chance or "genetic drift" and balanced polymorphism* may also influence the development of these isolates which are searched for so intensively and often studied so productively.

On the other hand, a survey of a disease in a mendelian population is expected to give an accurate measure of the incidence of the disease if the size of the sample surveyed is adequate and if ascertainment of cases is complete.

## CONSIDERATION OF SAMPLING ERRORS AND CONFIDENCE INTERVALS—ROCHESTER, MINNESOTA

As mentioned earlier, much of the material in this report came from a study of selected diseases in the resident population of Rochester, Minnesota. This population is not considered an isolate, nor does it contain significant isolates within it. The study, based mostly on the records of the Mayo Clinic, has the advantage of almost complete ascertainment of diagnosed cases for the community. Rochester, however, is a community of only 30,000 residents, and the chance fluctuation effect will be particularly marked in diseases of very low incidence. Some of the hereditary disorders affecting the nervous system have such a low incidence that the discovery of any case depends upon the level of the mutation rate in the population and the chance of settlement in the community of an affected family.

One of the main purposes of this paper is to provide estimates of the frequency of some diseases in the population of the United States. Since many of the estimates to be presented are based solely on the survey in Rochester, Minnesota, it should be a matter of concern as to how justifiable it is to extrapolate from a population of 30,000 to the population of the United States.

*A genetic term used to describe the situation in which a trait in the heterozygous condition has beneficial influence or reproductive superiority over the dominant and recessive homozygotes.

TABLE I. INCIDENCE AND AVERAGE ANNUAL INCIDENCE RATE PER 1,000 RESIDENT BIRTHS FOR SELECTED CONGENITAL ANOMALIES AND BIRTH INJURIES IN ROCHESTER, MINNESOTA (1945-1954, INCLUSIVE) AND THE ESTIMATED ANNUAL BIRTH INCIDENCE IN THE UNITED STATES BASED ON THESE RATES

| | ROCHESTER, MINNESOTA, CASES IN 14,200 BIRTHS AMONG LOCAL RESIDENTS, 1945–1954 | | | ESTIMATED NUMBER BORN IN U.S.A. ANNUALLY† | |
|---|---|---|---|---|---|
| | NUMBER | INCIDENCE PER 1,000 BIRTHS | | NUMBER | 95 PER CENT CONFIDENCE INTERVAL* |
| | | RATE | 95 PER CENT CONFIDENCE INTERVAL† | | |
| Congenital hydrocephalus | 16 | 1.1 | 0.5–1.7 | 4,700 | 2,100–7,200 |
| Dysraphias | 9 | 0.6 | 0.3–1.2 | 2,500 | 1,300–5,100 |
| Mongolism | 14 | 1.0 | 0.5–1.5 | 4,200 | 2,100–6,400 |
| Other perinatal brain syndromes-"cerebral palsy" | 9 | 0.6 | 0.3–1.2 | 2,500 | 1,300–5,100 |

*If it could be assumed that the United States is randomly represented by the Rochester data, there are 19 chances in 20 (95 per cent confidence interval) that the true rate for the United States lies within the range given. (See text for further details.)

†In 1956, there were 4,237,000 births in the Continental United States.

For fairly prevalent diseases, and assuming complete ascertainment of cases and an even geographic distribution, we can make use of sampling theory to draw conclusions from the sample about the total population. By use of the binomial distribution,[5] "confidence intervals" can be computed which provide an upper and a lower limit and which indicate the range of expected number of cases in a finite population. For convenience, a 95 per cent confidence interval has been adopted here which means that if the assumptions above are correct, the true value in the population at large could be expected to fall 19 out of 20 times between the limits which are given.

For many of the disorder to be described, none, one, or only a few cases were seen among residents of Rochester during the 10 years covered in the study. In such instances (where there were fewer than 30 cases), two-tailed confidence intervals have been computed by assuming that the number of cases in the sample follows a Poisson-like distribution.[6]

*Footnotes for Table II*

*For age-adjusted rate, if available; otherwise for crude rate.

†Data for 1927 through 1947; MacLean et al., used 25,000 as the average population of Rochester, Minnesota during this period.

‡The Rochester, Minnesota, data for these diseases may not be representative of the United States because of variations in geographic distribution. (See text.)

§The Rochester, Minnesota, data for these diseases are not considered sufficiently accurate to estimate the incidence in the United States population. (See text.)

‖Estimates for these disorders are subject to appreciable chance fluctuation. (See text.)

¶Rochester, Minnesota population was 29,885 on April 1, 1950.

#United States population in 1958 estimated at 170,000,000.

TABLE II. INCIDENCE AND AVERAGE ANNUAL INCIDENCE RATE PER 100,000 OF SELECTED NEUROLOGIC DISEASES FOR RESIDENT POPULATION OF ROCHESTER, MINNESOTA (1945-1954, INCLUSIVE); ESTIMATES OF ANNUAL INCIDENCE IN THE UNITED STATES BASED ON THESE DATA

| DISEASE | ROCHESTER, MINNESOTA ¶ | | | | ESTIMATED FOR UNITED STATES POPULATION# | |
|---|---|---|---|---|---|---|
| | | RATE (NEW CASES/100,000/YEAR) | | | | |
| | NO. OF CASES 1945–1954 | OBSERVED | AGE ADJUSTED | 95 PER CENT CONFIDENCE INTERVAL* | NO. OF CASES ANNUALLY | 95 PER CENT CONFIDENCE INTERVAL FOR ESTIMATED NUMBER OF CASES |
| Convulsive disorders (all types) | 89 | 29.8 | 30.8 | 24.5–37.1 | 53,000 | 42,000– 63,000 |
| Grand mal, primary | 25 | 8.4 | 9.1 | 6.0–13.2 | 15,000 | |
| Grand mal, secondary | 25 | 8.4 | 8.4 | 5.4–12.4 | 14,000 | |
| Petit mal | 9 | 3.0 | 3.3 | 1.6– 6.1 | 6,000 | |
| Psychomotor | 8 | 2.7 | 2.9 | 1.3– 5.5 | 5,000 | |
| Focal motor and sensory | 19 | 6.4 | 6.2 | 3.7– 9.7 | 11,000 | |
| Miscellaneous or unclassified | 3 | 1.0 | 1.1 | 0.2– 3.0 | 2,000 | |
| Multiple sclerosis† | 26 (for 21 years) | 5.0 | | 3.2– 7.2 | ‡ | |
| Acute optic neuritis | 15 | 5.0 | | 2.8– 8.2 | ‡ | |
| retrobulbar | 8 | 2.7 | | 1.2– 5.3 | | |
| papillitis | 7 | 2.3 | | 0.9– 4.8 | | |
| Amyotrophic lateral sclerosis | 5 | 1.7 | | 0.5– 3.9 | 2,900 | 900– 6,600 |
| Parkinson's disease (all types combined) | 71 | 23.8 | 20.0 | 14.9–25.1 | 34,000 | 25,000– 43,000 |
| Combined system disease | 10 | 3.3 | | 0.5– 1.8 | 5,600 | 900– 3,100 |
| with pernicious anemia | 8 | | | | | |
| without pernicious anemia | 2 | | | | | |
| C.N.S. neoplasms (all types) | 56 | 18.8 | 17.3 | 12.4–22.1 | | |
| primary brain | 25 | 8.4 | 7.7 | 4.9–11.6 | 15,000 | 11,000– 24,000 |
| pituitary | 5 | 1.7 | 1.5 | 0.5– 3.9 | | |
| primary spinal cord | 8 | 2.7 | 2.5 | 1.2– 5.3 | 4,200 | 2,000– 9,000 |
| intracranial and intraspinal metastatic | 18 | 6.0 | 5.6 | 3.2– 9.0 | § | |
| Tic douloureux | 13 | 4.3 | 4.0 | 2.3– 7.4 | 6,800 | 3,900– 13,000 |
| Myasthenia gravis | 1 | 0.3 | | 0.01–1.9 | 600§ | |
| Hereditary diseases | | | | | | |
| Muscular | | | | | | |
| muscular dystrophy (facio-scapulohumeral type) | 2 | 0.7 | | 0.1– 2.4 | 1,100‖ | |
| myotonic dystrophy | 0 | 0 | | 0.0– 1.2 | ‖ | |
| myotonia congenita (Thomsen's disease) | 0 | 0 | | 0.0– 1.2 | ‖ | |
| Neuromuscular | | | | | | |
| infantile progress muscular atrophy (Werdnig-Hoffmann's disease) | 1 | 0.3 | | 0.01–1.9 | 600‖ | |
| peroneal muscular atrophy (Charcot-Marie-Tooth) | 0 | 0 | | 0.0– 1.2 | ‖ | |
| Other hereditary diseases | | | | | | |
| Huntington's chorea | 1 | 0.3 | | 0.01–1.9 | 600‖ | |
| Hereditary cerebellar and spinocerebral ataxia | 0 | 0 | | 0.0– 1.2 | ‖ | |
| Hepatolenticular degeneration (Wilson's disease) | 0 | 0 | | 0.0– 1.2 | ‖ | |
| Dystonia musculorum performas | 0 | 0 | | 0.0– 1.2 | ‖ | |
| Infectious diseases | | | | | | |
| Herpes zoster | 248 | 83.0 | | 49.6–116 | 140,000 | 84,000–197,000 |
| Infectious neuronitis (Guillain-Barré syndrome) | 3 | 1.0 | | 0.2– 2.9 | 1,700 | |

(*For footnotes, see opposite page.*)

TABLE III. PREVALENCE AND AVERAGE PREVALENCE RATES PER 100,000 POPULATION FOR SELECTED NEUROLOGIC DISEASES IN RESIDENT POPULATION OF ROCHESTER, MINNESOTA, ON JAN. 1, 1955; ESTIMATES OF PREVALENCE IN THE UNITED STATES BASED ON THESE DATA

| DISEASE | ROCHESTER, MINNESOTA¶ | | | | ESTIMATED FOR UNITED STATES POPULATION# | |
|---|---|---|---|---|---|---|
| | NO. OF CASES ON JAN. 1, 1955 | RATE (CASES 100,000) OBSERVED | RATE (CASES 100,000) AGE ADJUSTED | 95 PER CENT CONFIDENCE INTERVAL* | NUMBER | CONFIDENCE INTERVAL |
| Convulsive disorders (all types) | 109 | 365 | 376 | 307–445 | 639,000 | 522,000–757,000 |
| Grand mal, primary | 50 | 107 | 172 | 125–219 | 292,000 | |
| Grand mal, secondary | 19 | 64 | 68 | 42–105 | 116,000 | |
| Petit mal | 6 | 20 | 23 | 9– 48 | 39,000 | |
| Psychomotor | 19 | 64 | 62 | 37– 98 | 105,000 | |
| Focal motor and senory | 13 | 44 | 43 | 23– 74 | 73,000 | |
| Miscellaneous or unclassified | 2 | 7 | 8 | 1– 26 | 14,000 | |
| Multiple sclerosis† | 18 | 55 | | 32.0– 85.4 | ‡ | |
| Amyotrophic lateral sclerosis | 2 | 6.7 | | 0.8– 24 | 11,000‖ | |
| Parkinson's disease (all types combined) | 56 | 187 | 157 | 112–201 | 266,000 | 190,000–342,000 |
| postencephalitic | 6 | 20 | | | | |
| with arteriosclerosis | 16 | 54 | | | | |
| without recognized arteriosclerosis | 34 | 114 | | | | |
| Combined system disease | 8 | 26.4 | | 11.5– 52.5 | 45,000 | 20,000– 89,000 |
| with pernicious anemia | 8 | | | | | |
| without pernicious anemia | 0 | | | | | |
| C.N.S. neoplasms (all types combined) | 22 | 73.6 | 68.6 | 42.2–105.4 | | |
| primary brain | 12 | 40.2 | 37.1\ | 25.0– 77.6 | 77,000 | 42,000–130,000 |
| pituitary | 3 | 10.0 | 8.9/ | | | |
| primary spinal cord | 4 | 13.4 | 12.9 | 3.4– 33.6 | 22,000 | 6,000– 56,000 |
| intracranial metastatic | 3 | 10.0 | 9.7 | 1.9– 28.8 | § | |
| Syringomyelia and syringobulbia | 1 | 3.3 | | 0.1– 19 | 5,600‖ | |
| Myasthenia gravis | 1 | 3.3 | | 0.1– 19 | 5,600‖ | |
| Hereditary diseases | | | | | | |
| Muscular | | | | | | |
| muscular dystrophy (facioscapulohumeral type) | 2 | 6.7 | | 0.8– 24 | 11,000‖ | |
| myotonic dystrophy | 1 | 3.3 | | 0.1– 19 | 5,600‖ | |
| myotonia congenita (Thomsen's disease) | 1 | 3.3 | | 0.1– 19 | 5,600‖ | |
| Neuromuscular | | | | | | |
| infantile progress muscular atrophy (Werdnig-Hoffmann's disease) | 1 | 3.3 | | 0.1– 19 | 5,600‖ | |
| peroneal muscular atrophy (Charcot-Marie-Tooth) | 0 | 0 | | 0.0– 3.7 | ‖ | |
| Other hereditary diseases | | | | | | |
| Huntington's chorea | 2 | 6.7 | | 0.8 –24 | 11,000‖ | |
| hereditary cerebellar and spinocerebral ataxia | 0 | 0 | | 0.0– 3.7 | ‖ | |
| hepatolenticular degeneration (Wilson's disease) | 0 | 0 | | 0.0– 3.7 | ‖ | |

*For age-adjusted rate, if available; otherwise for crude rate.

†Data for 1948, MacLean et al. used 33,000 as the population of Rochester, Minnesota for this year.[7]

‡The Rochester, Minnesota, data for these diseases may not be representative of the United States because of variations in geographic distribution. (See text.)

§The Rochester, Minnesota, data for these diseases are not considered sufficiently accurate to estimate the incidence in the United States population. (See text.)

‖Estimates for these disorders are subject to appreciable chance fluctuation. (See text.)

¶Rochester, Minnesota, population was 29,885 on April 1, 1950.

#United States population in 1958 estimated at 170,000,000.

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Wherever feasible, the rates for Rochester have been age adjusted to the age distribution of the United States as a whole and the age-adjusted rate (rather than the crude rate for Rochester) has been applied to the estimated 1958 population of 170,000,000 to obtain an estimate of the number of cases in the United States.

The confidence intervals are particularly broad (relative to the rate in the community) for diseases of very low frequency. This effect is illustrated in Tables I to III where confidence limits and, where appropriate, the frequencies in the United States have been estimated. These frequencies are computed from incidence values based on the number of cases among Rochester residents during 10 years (1945—1954, inclusive), and for prevalence values based on the surviving resident patients as of Jan. 1, 1955 ("prevalence day").

Since complete ascertainment of the Rochester cases cannot be assured, the Rochester incidence and prevalence rates should be considered minimal values.

The disorders included in this report are only a spotty representation of the field of neurology, but they were selected for several reasons. Most of them are diseases of unknown or uncertain etiology which seemed to be particularly good candidates for descriptive epidemiologic studies. A "good candidate" was one for which little or no incidence and geographic data were available and one for which such data seemed to hold promise of providing leads for experimental laboratory or definitive epidemiologic research. A few recognized traumatic and infectious diseases were included, often because of some special interest or in anticipation of the need for base-line data for future comparative studies in other populations. Some diseases known to be very uncommon were included because of a special request for such information from some clinical investigators or from one of the voluntary health associations. Unfortunately, at the time of the study, it was felt that it was beyond the resources or the field of interest of the study group to obtain representative statistics for vascular and some other diseases affecting the nervous system. It is hoped that the need for basic data on these important subjects, which is now so apparent, will result in correction of that condition in the near future.

Since only selected segments of neurology are represented in this material, no special clinical or etiologic classification has been followed.

## PRESENTATION OF THE ROCHESTER, MINNESOTA, SURVEY RESULTS

The birth incidence rates and the average annual incidence and prevalence rates for the total population are presented in Tables I to III. Confidence intervals and, where appropriate, estimates for the United States population have been included. Many of the data summarized here are available elsewhere in an earlier report on multiple sclerosis by MacLean and associates[7] and in reports by Kurland and associates on the epidemiology of amyotrophic lateral sclerosis, parkinsonism, neoplasms, cerebral palsy, and convulsive disorders.[1,4,8-10]

## CONGENITAL MALFORMATIONS AND BIRTH INJURIES

Although extensive coverage for this subject is available through official birth and death records, omissions and errors in reporting and combination of

numerous disorders within a single official rubric limits the availability of such statistics. No extensive geographic comparison in the United States has been made. A number of excellent surveys of birth and death records and reports of detailed consecutive examinations are available for this subject, but only a few can be reviewed here.

Penrose[10] has observed that the birth incidence rates in Europe for anencephaly and spina bifida (but not mongolism) are highest in Ireland and western Great Britain, and that they decrease as one proceeds eastward on the continent of Europe. Furthermore, McKeown and Record[11] reported a rather wide variation in the incidence of anencephaly in successive years in Scotland and also noted an apparent increased incidence of anencephaly among infants born in the winter months. To what extent these variations are due to some artifact in reporting and to what extent they are due to some unrecognized genetic or environmental cause is uncertain.

Microcephaly has come in for particular attention recently following several reports reviewed by Miller[12] on the apparent increased incidence following intrauterine irradiation. In the study by McIntosh and associates[13] of congenital defects in a New York population microcephaly was noted twice in 6,053 births.

In Rochester, Minnesota, there were 14,200 resident births during the 10 years of the study; 98 per cent of these deliveries were at St. Marys Hospital, and all infants were examined by staff pediatricians of the Mayo Clinic prior to discharge from the hospital. Several anomalies and birth injuries in the clinic records were included in the present study.

*Hydrocephalus and Dysraphia.*—Among Rochester, Minnesota, residents there were 25 cases of hydrocephalus at birth or within the first year of life in a 10-year period (1945-1954). Four of these were "suspect" cases. Of the 21 definite cases, 16 were diagnosed at the time of birth and 5 within the first year after birth.

Of the 16 patients (7 male, 9 female) with hydrocephalus at birth, 7 also had myelodysplasia. Four of the 16 were stillborn owing to the necessity of perforating the skull to deliver the fetus; 7 others died within the first few hours or days after birth; 2 others died a few months after birth. Of the 3 remaining (ages 1, 2, 4 years in 1955), all were so retarded that they were institutionalized. On the basis of the 16, the birth incidence rate would be about 1.1 per 1,000 total (live and stillborn) births (Table I); if the 4 who were stillborn are eliminated, the rate is 0.8 per 1,000 live births. In this small series, there was no indication of a seasonal or annual concentration of cases.

Of the 5 cases (2 male, 3 female) with hydrocephalus noted within the first year after birth, 2 were thought to be related to prematurity, one to cerebral hemorrhage at birth, one to meningitis after birth, and one to "cause unknown." Two of these 5 patients died before age 1 year, one died at age 9 years, one had "arrested" of her disease, and the other one was institutionalized.

There were 9 infants born with dysraphia during the 10-year period (rate 0.6 per 1,000 total births). One of the patients was born with meningoencephalocele and the others had meningocele or meningomyelocele; 7 of the 9 also had hydrocephalus.

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Five of the 9 died within a few days after birth. Four others were living, 2 (ages 1 and 2 years) being confined to a state institution, and 2 (ages 3 and 9 years) living at home; both of the latter were severely disabled with paralysis of the lower extremities and incontinence of the bladder.

In addition there were 3 other cases not arising locally or during the survey period in which a diagnosis of relatively mild myelodysplasia was made several years after birth.

Seven of the 16 newborn infants with congenital hydrocephalus also had obvious myelodysplasia. Although not specifically diagnosed as such, these probably had the Arnold-Chiari malformation as described by Russell.[14]

Dysplasias of the vertebrae are said to be present in about 25 per cent of all children, but most of these are minor and of no clinical significance.[15,16] Cranium bifidum is reported to be about one-sixth as frequent as clinically important spina bifida.[17] In the present series there were 8 patients with myelodysplasia and 1 with encephalodysplasia.

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It is not feasible to attempt a comparison of the birth incidence rate with statistics from a selected hospital series of cases. It is of interest, however, that in the series of dysplasias of the vertebrae studied at the Children's Hospital, Boston, the frequency was 1 in 4,150 patients (relative hospital admission rate)[18]; this low ratio (about one-third the birth incidence rate in Rochester) probably reflects the high mortality before infants could be transferred from obstetrical hospitals or home to the Children's Hospital.

In the study of congenital anomalies by McKeown and Record,[11] the rates per 1,000 total births from official death certificates in Scotland (1939-1946) were 1.38 for hydrocephalus, 0.46 for spina bifida, and 2.51 for anencephaly. In the report by Ingalls, Pugh, and MacMahon[18] on malformations of the central nervous system in 168,654 births in five Rhode Island maternity hospitals, the rate per 1,000 total births was 0.9 for hydrocephalus, 2.53 for spina bifida and meningocele, and 1.93 for anencephaly. Problems of definition and procedure make comparisons of these various rates difficult.

Ingalls, Pugh, and MacMahon[18] report an increase in the hydrocephalus birth rate with late maternal age and also indicated that on the basis of their data anencephaly and spina bifida may arise on the same basis and might be different causally from hydrocephalus. The frequent occurrence together of hydrocephalus and meningocele in our survey suggests that such an hypothesis is not correct.

Two other sources of data may be useful for general comparisons. McIntosh and his colleagues[13] in New York noted 5 cases of hydrocephalus (3 were stillbirths or neonatal deaths) in 6,053 births (0.8 per 1,000 births). Meningomyelocele or meningoencephalocele was noted in 7 births (3 stillbirths or neonatal deaths) or 1.2 per 1,000 births in this series. Because of the small series of cases, no conclusions can be drawn regarding the differences in birth rates between the Rochester, Minnesota, series and this New York series, although ascertainment of cases in the two series was probably comparable.

Gentry, Parkhurst, and Bulin[19] have reviewed the birth and associated death certificates for more than a million births in upstate New York from 1948—1955. Malformations of the central nervous system were noted in 2.0 per 1,000 births.

Of these, hydrocephalus accounted for 0.5, spina bifida and meningocele for 0.9, monstrosity for 0.4, and other disorders for 0.2 per 1,000 births.

It would appear that the rates given by Gentry, Parkhurst, and Bulin are appreciably lower than those from many other sources reviewed above. If the ascertainment of cases from different geographic divisions of the New York registration is equally complete (or incomplete), it might be possible to use such data for comparisons within different subdivisions of the New York population.

Although the over-all comparisons might suggest that the incidence of hydrocephalus was relatively high and dysraphia relatively low in Rochester, the size of the Rochester series and the differences in method may account for discrepancies.

*Mongolism.*—During the 10 years, 14 children (12 males, 2 females) with mongolism (congenital acromicria) were born to resident parents in Rochester, Minnesota; 7 (5 males, 2 females) died during the study period. The birth incidence rate for the period of study is 1.0 per 1,000 live births. In each case the diagnosis was made during the infant's initial admission at the time of birth or suspected and subsequently confirmed on later examinations. There were no clear indications of any concentration of cases in any one year or in any particular season during the period of study.

As Øster[20] and others[21,22] have pointed out, the frequency of mongolism may be expressed as birth incidence rates, as prevalence in the total population, as a ratio among the inmates of institutions for the mentally retarded, or as a ratio among pediatric clinic patients.

The ratio of mongol births to total births would seem to provide the best means of relating the cases to the most specific population "at risk." If the diagnosis can be made at or near birth, this ratio can be obtained accurately. According to Øster,[20] in 25 per cent of the cases the diagnosis may not be made until months after birth, and in communities where domiciliary births occur frequently, the delay may be even greater and the diagnosis missed more frequently. Domiciliary births provide a lower ratio of mongol to total births in Record and Smith's[22] study than did hospital births, in spite of the older average age of mothers who delivered at home. This lower birth ratio was presumed to be due to missed diagnoses at birth and the higher death rate among mongols in early life who, in a domiciliary situation, might not be identified.

In every case in the present study the diagnosis was made or suspected at birth and clinically confirmed during subsequent visits to the clinic. It is likely that few, if any, resident cases in which this serious affliction was present would not have been observed by the pediatric specialists at the clinic.

Numerous birth rates for mongolism have been reported by different investigators. Record and Smith[22] reported 1.1 mongols per 1,000 total births in Birmingham, England. Øster[20] reviewed the reports of eight hospital series which gave frequencies ranging from 0.5 to 3.4 per 1,000 births but rejected the highest (Beidleman[23]) and the lowest (Stevenson, Worcester, and Rice[24]) which showed a remarkable discrepancy considering that they were derived from the same hospital (Boston Lying-in Hospital) for an overlapping period of years. The incidence of the six other series ranged from 1.1 to 2.1 (mean 1.7) per 1,000

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births. To these figures may be added an estimate by Øster* and that of Carter and MacCarthy.[25] The last investigators obtained their data from several London maternity hospitals and noted that the birth ratio averaged 1.58 and was highest (2.1 and 1.6 per 1,000) in the two hospitals where the staffs were particularly interested in mongolism. They estimated the incidence in England as approximately 1.6 per 1,000 births by correcting for differences in maternal age distribution in their hospital births.

In the report by McIntosh and associates referred to earlier,[13] there were 11 cases in which the diagnosis was made during the first year following birth of the 6,053 infants. The rate 1.8 per 1,000 births is similar to that reported from the European studies. In Gentry's study of birth and death certificates in upstate New York,[19] the rate was only 0.3 per 1,000 births; the reasons given above for underreporting would seem to offer a satisfactory explanation of this discrepancy, but it is disconcerting that only about one-third to one-half of the expected number of cases of mongolism (on the basis of the other reports) were included in the official birth and death reports of upstate New York.

If no cases were missed among the newborn in Rochester, Minnesota, during this period, there is a suggestion of a lower birth incidence in this population than in most of the others reported. It is believed that the risk of a child being born with this defect is greater among the youngest and among the oldest mothers.[26,27] The age distribution of Rochester mothers available for 1951, was compared to that of the United States national average. In Rochester 5.8 per cent of the births occurred in mothers under 20 years of age (11.5 per cent, United States), and 6.5 per cent in those aged 35-39 years (8.1 per cent, United States), and there was no significant difference in the rates for ages 40 years and over.

In the present series and in most large series reported in the literature, there is a preponderance of affected males.[26-28] Part of this, according to Record and Smith, is due to the relatively low survival rate for the female patients and the subsequent preferential selection of males for admission into institutions or pediatric clinics from which many of the sex ratio statistics are derived. In the present study, there were 12 males and 2 females. Since the diagnoses were made in the immediate neonatal period, such selection does not apply. However, the number of cases is not large enough to rule out chance as a factor in this ratio.

Engler[28] claims that mongolism is increasing in the population and states that "difficult living conditions, increased rate of sickness, and above all, increasing popularity of contraceptives, abortifacients, and curettage, must also be held responsible." No statistical evidence is given to support this view of any increase in mongolism rate; our data provide no evidence of any change in the annual incidence over the 10-year period in this community.

*Cerebral Palsy.*—The birth incidence rate for cerebral palsy in the resident population of Rochester, Minnesota, was 0.6 per 1,000 births and the prevalence

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*The actual value Øster found was 0.84 per 1,000 for this entire series over a 25-year period. However, he preferred the rate of 1.6 per 1,000 for the period 1938-1948 from the hospital in which there was particular interest and presumably more accurate diagnosis of this problem. He felt that this was still a minimal figure since selection of maternal admissions favored younger primipara in the hospitals from which the statistics were derived.[20]

rate was 0.7 per 1,000 total population, or 1.6 per 1,000 population under the age of 2 years. The rate in Rochester is only one-third to one-tenth of that estimated in several reported community surveys for cerebral palsy. Although the discrepancy may have been due, in part, to differences in method of case collection, the principal reason relates to the view of what should constitute "cerebral palsy" cases in retrospective field research. In the Rochester study the following definition of "cerebral palsy" was adopted: those disorders of unknown etiology arising during the perinatal period (from conception to the end of the neonatal period) in which motor dysfunction due to brain damage is recognized prior to the end of infancy. Disease entities of a progressive nature, such as epiloia or Tay-Sachs cerebromacular degeneration, or well-recognized symptom complexes affecting motor function, such as hydrocephalus, mongolism, or encephalodysplasia, are not included in this cerebral palsy category. The constituents of the cerebral palsy category still form a heterogeneous combination, and the diagnosis is essentially one of exclusion.

Unfortunately, there are few reliable data on geographic distribution of this heterogeneous group of disorders, and conclusions drawn by others that some differences in rates reflect differences in obstetrical care or racial predisposition are unfounded. The reader is referred to a detailed discussion of the problems of definition and field research of cerebral palsy in which comparisons of clinical types of motor dysfunction are also presented.[1]

It is believed that the procedure followed in this report of a separate statistical analysis for well-defined disease entities and syndromes affecting motor function will result in a residuum of the ill-defined and heterogeneous group of disorders (cerebral palsy) which are amenable to improved clinicopathologic correlations and epidemiologic research. Ultimately, it is hoped, such research will entirely eliminate the cerebral palsy diagnosis by defining the nature of its constituents and lead to prevention and control of the numerous disease entities included in the present-day cerebral palsy category.

### CONVULSIVE DISORDERS

Classifications of convulsive disorders have been formulated on the basis of symptomatic seizure patterns, known or presumed causes, and characteristic electroencephalographic (EEG) patterns; in the Rochester study a symptomatic classification was adopted. Most of the earlier estimates of the incidence of convulsive disorders have been derived from the same unrepresentative sources previously mentioned. Available estimates on the basis of Selective Service and military records for young men suggest that the prevalence of epilepsy is about 4 to 6 per 1,000 persons in the United States.

The frequency of convulsive disorders in Rochester was determined by the procedure described earlier. Details of method and definitions for the convulsive disorders have been presented elsewhere[29] but will be reviewed briefly along with some of the principal results of that study. The symptomatic classification adopted is shown in Tables II and III.

Patients who had only one convulsive or epileptic episode were considered as "suspect" and not as definite cases of epilepsy, even though the convulsion

was a typical attack.* If two or more episodes were recognized and the physician, on the basis of the history and the examination (which may or may not have included EEG), recorded the diagnosis as one of the epilepsies or under an acceptable synonym, the case was considered "clinically acceptable." The EEG was considered only an adjunct to examination by the clinician making the diagnosis; the report of cerebral dysrhythmia in the absence of clinical findings of epilepsy did not result in a "case" for this study any more than a normal EEG in a patient with an appropriate history would rule out such a diagnosis.

For the incidence count, only individuals who were local residents at onset during the period 1945 to 1954, inclusive, were included. Patients who were residents in the community on Jan. 1, 1955, were included in the prevalence count but only if they had had their most recent convulsive episode within the past 5 years or had been on anticonvulsant medication during that time.

*The Frequency in Rochester.*—Patients with febrile convulsions, even those with only single episodes, were included, but in a separate category. Exclusive of the category of febrile convulsions, 194 "clinically acceptable" patients were observed during the 10-year period of the study: 89 had their first episode during the 10 years of the study so that the average annual incidence rate for the community was 29.8 per 100,000 population (30.8 per 100,000 population, age adjusted to the United States population). The rate was higher for males (41.4 versus 20.8 for females) for all types of seizures combined and for most of the individual categories. Primary and secondary grand mal epilepsy each accounted for about one-fourth of the new cases. For all four categories of convulsive disorders combined, the incidence rate was highest in the age group under 5 years (152.0 per 100,000 population), and dropped to a low level (4 to 20 per 100,000 population) between 20 and 70 years of age. After 70 years of age, when it is confined to secondary grand mal and focal seizures, the rate began to rise sharply again (74 per 100,000 population for those aged 80 years and over).

Primary grand mal and petit mal were found to have their highest rates of incidences in childhood and early adolescence. Various anomalies and birth injuries were in part responsible for the high rates in infancy and early childhood, whereas vascular disease and brain tumors (including metastatic disease) were the precipitating factors in the older age groups. The occurrence of convulsions in adults with tumor or cerebral vascular disease may be relatively underreported since the suspected underlying diagnosis alone rather than some of the major clinical symptoms may have been emphasized on the diagnostic records.

The prevalence rate for convulsive disorders (again excluding the category of febrile seizures) in this community was 365 per 100,000 population (498 for males and 261 for females). Higher rates for males prevailed for all types combined and for each type separately. The prevalence rates for all types combined changed very little for age groups between 10 and 60 years of age.

It was felt that the category of febrile convulsions merited separate analysis. During the period of the study there were 101 infants and young children (59

*A convulsive "episode" (definition for this study) may be either a single seizure or several such seizures interrupted by brief periods of relative calm which may occur throughout the period of the disturbance, such as might be noted in a single day of febrile illness.

males, 42 females) who had one or more convulsive episodes associated with febrile illnesses. One episode only was recorded for 76 of these patients. An additional 15 patients had two episodes, and the remainder had three or more recorded convulsive episodes. Roseola infantum was recognized as an associated illness in 14 per cent of the seizures. The median age at onset in this total group was 18 months. It is likely that this category of febrile convulsions is appreciably underreported as compared to the other convulsive disorders since single episodes may not be observed or cases seen by the physician in general practice may not be considered sufficiently serious to warrant obtaining an EEG or a specialist's opinion.

*Estimated Frequencies for the United States.*—Tables II and III present the incidence and prevalence estimates for the United States population based on the data from Rochester. The appropriate adjustments in those tables for age and chance fluctuation are included.

The Rochester survey represents an initial attempt at obtaining frequency figures on convulsive disorders on the basis of a total population survey. The small size of the Rochester population is a handicap in this study, but this is offset to a great extent by the outstanding medical coverage of the population and the excellent system of medical records in the Mayo Clinic and the affiliated hospitals.

Some information on family histories of seizures was available, but it is felt to be of little value because of the absence of any statement about this aspect on many of the charts and the lack of assurance concerning uniformity in the questioning. There is an increasing amount of evidence, which cannot be reviewed here, suggesting that in some types of convulsive disorder, genetic predisposition is important if not critical. Even though the figures derived from the application of the Rochester rates to the total United States 1957 population are gross estimates, it is felt that they are as accurate as any available at this time. Further surveys of this type are contemplated so that more detailed population comparisons may possibly be made.

## MULTIPLE SCLEROSIS

This disorder has been the subject of several recent population surveys and reviews.[30,31]

An interesting and still unexplained feature of this disorder is its geographic distribution. The disorder is rare in the populations of the tropics and subtropics as compared with the populations of temperate climates. Mortality rates for multiple sclerosis are higher for Canada and the northern United States than for the southern United States. Morbidity surveys indicate that prevalence rates in Boston, Massachusetts, and Winnipeg, Manitoba, are about six times higher than in New Orleans, Louisiana, and about three or four times higher than in Charleston County, South Carolina.[30,32] There is no definite indication that prevalence rates for multiple sclerosis differ in urban and surrounding rural areas. Within the communities studied, the disease appears to be randomly distributed in the population at large with respect to occupation, education, head or back trauma, housing, sanitary facilities, history of past infections and

immunizations, and, in a general way, to the quantity of fat in the diet. In Winnipeg, the illness was equally prevalent in the three predominant national groups—English, French, and Ukrainian. The rate among Negroes in Boston is higher than among Negroes in New Orleans and suggests that some feature of geographic exposure and not of race or nationality is crucial in the development of the illness. Studies still in progress suggest that although multiple sclerosis occurs in the population of Japan, it may not be as prevalent as in North America and, perhaps, does not vary from north to south in Japan to the extent that it does in North America.[33,34]

In spite of the geographic variations in the disease and the suggestion that this factor is related to some condition associated with climate, there is no indication that incidence varies with season or usual weather conditions.[35]

The disease occurs in both sexes, perhaps slightly more often in females. First symptoms develop predominantly in younger adults, and relatively few cases occur before age 15 years or after age 50 years. There is a suggestion that the median age at onset is slightly less in those communities with the higher incidence rates.[36] The effect of pregnancy on multiple sclerosis is still unsettled, although recent evidence suggests that onset and exacerbations occur no more often in pregnant than in nonpregnant patients.[30]

It is uncertain whether persons who develop multiple sclerosis have fewer exacerbations if they reside in an area with a milder climate.[36] An effort was made to determine whether members of the U.S. Armed Forces who developed retrobulbar neuritis from 1942 to 1946, inclusive, showed any difference in the frequency of subsequent multiple sclerosis which might be associated with place of residence in the intervening years. The study has not been completed successfully because only about 10 per cent of the patients with retrobulbar neuritis developed multiple sclerosis 10 or 15 years later in contrast to the expected 40 or 50 per cent based on reported clinical experiences.[37] Other means of studying the geographic effect on prognosis will have to be explored.

The average annual incidence rates were determined for a decade in several cities in the United States and Canada. These showed no particular trend or undue fluctuation with time.

The highest prevalence rates for multiple sclerosis reported in the United States and Canada have been in several small communities which were intensively studied (Rochester, Minnesota; Kingston, Ontario; and Missoula, Montana).[7,38,39] In these communities, the prevalence rates ranged from 53 to 64 per 100,000 population. This is similar to the prevalence reported in an intensive, long-term study in Denmark (58 per 100,000 population),[40] and one in a rural area of Northern Scotland[41] (55 per 100,000 population). In a population survey in Northern Ireland,[42] the computed prevalence rate was 41 per 100,000 population for the total population. The rates for the small communities in the United States and Canada, for North Scotland, and for Denmark are somewhat higher than those reported for Winnipeg (42 per 100,000), Boston (41 per 100,000), and North Ireland (41 per 100,000), but it is believed that differences in the intensity of case-finding procedures account for these differences in rates.

On the basis of the data available and allowing for persons with early and undiagnosed but potentially handicapping disease, it would appear that the prevalence in the United States ranges from about 10 per 100,000 population in the Deep South to about 50 to 75 per 100,000 population in the North. Multiple sclerosis probably plays some role in the deaths of about 2,500 to 4,000 persons per year in the United States (of these, about 1,500 per year are reported as underlying and about 300 as contributory causes of death in the official statistics). The long average duration after onset (about 20 to 25 years)[36,43] accounts for the high prevalence as compared to the low incidence and mortality figures. It is estimated that there are in the United States, at any one time, about 75,000 to 100,000 persons with clinically identifiable multiple sclerosis.

The question of whether genetic predisposition plays an important role in multiple sclerosis is still unsettled.[30,31,41,44] The concurrence of the disease in twins is less than would be expected of a hereditary disease, but the incidence among other family members of patients is said to be higher than in the general population.[45] Further study is necessary to establish a constitutional predisposition for multiple sclerosis, but it is generally agreed that an exogenous factor is of prime importance. There is little evidence of selectivity for any race or nationality in any particular locality, and there seems to be an almost random distribution of cases within most of the carefully surveyed communities or districts. This local random distribution presents difficulties in the attempt to derive biologic inferences from the reported pattern of distribution or to develop a suitable hypothesis of etiology which would serve as a guide for appropriate clinical or laboratory research.

In spite of these shortcomings, the data presented in this review may remove a number of erroneous concepts of cause, and it is reasonable to expect that future etiologic hypotheses based on clinical or laboratory observations should be consistent with the known distribution of the disorder in human populations.

### ACUTE RETROBULBAR NEURITIS

In the Rochester survey, there were 8 patients with acute retrobulbar neuritis. This disorder is characterized by the development of complete or partial loss of vision, with scotoma (usually central or centrocecal) without visible involvement of the optic nerve head. In 5 patients (4 female, 1 male), the disorder was associated with multiple sclerosis. In 4 of these, the onset occurred between ages 19 and 25 years; in the other patient (female), the onset of symptoms occurred at age 42 years. In two of the other 3 patients, the cause was unknown, but incipient multiple sclerosis was suspected; the third patient had bilateral retrobulbar neuritis which accompanied measles encephalitis.

### ACUTE OPTIC NEURITIS (PAPILLITIS)

There were 8 patients (1 male, 7 female) papillitis in which the complaint may be the same as in retrobulbar neuritis but in whom the nerve head is visibly inflamed. Seven of the 8 cases occurred locally during the study period. In

none of the patients was multiple sclerosis an associated diagnosis. The ages at onset varied considerably (4 through 57 years), and 7 of the patients were still alive on prevalence day. In most instances, no cause for the optic neuritis could be ascertained. One patient had almost complete recovery of the visual loss; all others had moderate to severe loss of visual acuity.

The experience of Taub and Rucker[37] in their observation of the progression of retrobulbar neuritis to multiple sclerosis has already been referred to. The possibility that the prognosis is not always as serious as they reported has also been suggested in the preceding section on multiple sclerosis.

The incidence rates for retrobulbar neuritis and papillitis in Rochester are presented in Table II.

### AMYOTROPHIC LATERAL SCLEROSIS

The clinical diagnosis of amyotrophic lateral sclerosis (ALS) depends upon evidence of involvement of lower motor neurons and usually but not necessarily with involvement of upper motor neurons. At times, there is pathologic involvement of other structures of the central nervous system without evident clinical effects.[46] Very few cases in any large series of the syndrome of amyotrophic lateral sclerosis (either clinical or pathologic) are found to be due to syphilis, identifiable vascular abnormalities, or other specific causes. Almost all cases must be classified as "cause unknown."

Progressive muscular atrophy or progressive bulbar palsy is considered as the essential component of ALS. It has been suggested that ALS may be a member of a "continuum" of heredodegenerative disorders of the nervous system and that it is inherited as a dominant trait.[47]

Official United States mortality figures for the motor neuron disease rubric (almost 95 per cent of the deaths in this rubric are from progressive muscular atrophy, progressive bulbar palsy, or ALS) are almost as high (about 1,200 per year) as annual mortality from multiple sclerosis. The relatively short duration of life after onset of the symptoms of ALS allows for a lesser accumulation of cases in a period such as a year; and although incidence and mortality rates may be fairly close to those for multiple sclerosis, the prevalence rates for ALS are only about one-tenth to one-fifteenth of that for multiple sclerosis in populations of the temperate zones.

A comparison of age-adjusted mortality rates for regions of the United States, for Canada, Australia, Japan, and for six European countries reveals the average annual mortality rates in these widely separated countries to be surprisingly uniform.[4] (All rates when age-adjusted were between 0.75 and 0.95 per 100,000 population.) It is estimated that the prevalence ratio in these countries is about 4 to 6 per 100,000 population and that the incidence and death rates, corrected for underreporting, are about 1.4 per 100,000 population per year. Similar incidence and prevalence rates were also noted for the Rochester, Minnesota, resident population based on the local patients seen at the Mayo Clinic over a 10-year period.

In the United States, at any one time, it is estimated (from Rochester and other data) that there are about 5,000 to 10,000 persons with clinically identi-

fiable ALS, of whom about 65 per cent are males. Each year about 2,000 to 3,000 persons are newly affected, and a large percentage of these are represented in the subsequent official mortality statistics.

The mean age at onset for this disorder is about 45 years, first symptoms occurring between the ages of 35 and 60 years in two-thirds of patients.

Death rates and incidence rates for ALS are about 1.7 times greater for males than for females. It has been suggested that a gene with "modifying" capabilities for this disorder is present on the X chromosome and that females, having two X chromosomes, have a greater natural protection against developing clinical ALS, even if they have inherited or have been subject to a mutation of the gene on the autosome which could result in ALS.[4]

Mortality rates for ALS do not show an appreciable geographic variation in the continental United States. The official rates appear to be higher for the white population than for Negroes, but morbidity surveys of this item have not been completed.

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In the Chamorro population of the isolated Mariana Islands of the western Pacific and among Chamorros who have migrated to the continental United States in recent decades, classic ALS is about 100 times as prevalent as in other populations of the world. In the Mariana Islands, ALS is highly prevalent among the Chamorros only and not among other ethnic groups residing in the same islands. A comparison of many environmental features of patients and unaffected adults in the Mariana Islands has not consistently demonstrated any exogenous factor which might be identified as etiologically important.[48]

The large majority of patients interviewed in clinical studies in the United States deny other cases in the family. Mulder and Kurland[47,49] have reported two large series in which 6 and 9 per cent, respectively, of patients interviewed reported that others in the family were affected. In these pedigrees and among 38 family histories personally collected or reported in the literature (exclusive of the Chamorros), the disease appears to occur as a dominant genetic trait with incomplete penetrance. Numerous necropsy specimens from Guam and several from familial cases among Caucasians in the United States which have come to the attention of this writer cannot be distinguished from classic cases of ALS. However, several other familial cases have recently been described[46] which suggest that some of the hereditary cases seen in the United States show typical pathologic changes in anterior horn cells and lateral columns but also have evidence of some demyelination in the posterior and dorsal spinocerebellar columns.

The uniform geographic distribution (aside from the genetic "isolate" of the Mariana Islands) suggests that a significant etiologic factor in ALS is widespread and evenly distributed with respect to countries with large populations. It is conceivable that in large populations the combined effect of a mathematically regular mutation rate with a subsequent random gene frequency and an average rate of gene penetrance could be responsible, after many generations, for the almost equal incidence of this disease in such large populations.[4]

In small "isolates" the accidental occurrence or introduction of an individual with a highly penetrant genetic endowment may result under suitable circumstances of genetic drift or polymorphism in an exceedingly high proportion of the

small population being affected in later generations. It is believed that a combination of fortuitous circumstances beginning about 250 years ago in Guam accounts for the high prevalence of ALS among the Chamorros today.[4] The fascinating story of the early observations of ALS among the people of the Mariana Islands[50,51] and the reasons it may have developed into a leading cause of death in that population have been covered in other publications.[4,48]

The possibility that there are two principal forms of ALS—hereditary and sporadic—has been considered. However, my opinion is that classic ALS is due to a genetic mechanism but, in many cases, the gene is inherited without manifestation of the disease (i.e., incomplete penetrance) perhaps because of the absence of a precipitating environmental factor or because of the presence of genes in other loci capable of producing an enzyme or metabolite which can substitute for the specific neurochemical agent which has been hypothesized as critical in the development of this disorder.[4]

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### PRIMARY LATERAL SCLEROSIS

The syndrome of primary lateral sclerosis is found in association with a number of genetic disorders (familial spastic paraplegia and cerebellar ataxia) and in some disorders of uncertain cause such as multiple sclerosis and syringomyelia. Incidence data for the syndrome would therefore reflect the incidence of numerous other disorders, and no attempt will be made to present them.

In Rochester there were 2 patients, both females, aged 45 and 54 years at onset, in whom a diagnosis of primary lateral sclerosis alone was made. Neither of them had her onset during the survey period, and only one survived to prevalence day. The other patient was found at necropsy to have demyelinization of the lateral columns and a malignant hemangioma of the brain.

### PARKINSONISM

There are remarkably few reliable population statistics for this syndrome, which ranks as one of the most prevalent disorders of the central nervous system. The ease of recognition and treatment by the physician in general practice, the insidious onset, and the acceptance by much of the profession and the public of mild parkinsonism as an almost normal accompaniment of advanced age, all complicate population survey procedures. Two reports, one based on a postal inquiry of physicians in Leeds, England,[52] and the other on a survey of clinics and specialists in Sweden,[53] provide prevalence rates which are considered too incomplete to warrant their use for comparative studies.

Since parkinsonism, when present, is so frequently considered as coincidental rather than an underlying cause at the time of death, it should come as no great surprise that only about 20 per cent of deceased parkinsonism patients in one community studied had the diagnosis listed on the death certificates.[8] The use of mortality data for comparative studies is of limited value. Official death rates for parkinsonism are similar in various regions of the United States and Canada suggesting that the causative factor or factors are widely but fairly evenly distributed. However, because only a fraction of all the affected who die are repre-

sented in the official statistics, this conclusion is valid only if the reports are equally complete for Canada and for each of the regions of the United States.

Statistics for parkinsonism have been obtained for the resident population of Rochester, Minnesota, and are summarized in Tables II and III. The details of definition and classification are reported elsewhere.[8]

On the basis of the Rochester data, it is estimated that each year about 1 person per 4,000 in the total population and about 1 per 1,000 in the population aged 50 years and over are *newly* affected. For the United States this represents an incidence of about 34,000 new cases per year (95 per cent confidence interval 25,000 to 43,000).*

Few of the new cases in Rochester developing in the previous 10 years appear to be associated with encephalitis or with identifiable toxic agents. The remaining cases were classified as "associated with arteriosclerosis" or "without recognized associated conditions" (iodiopathic). Arteriosclerosis, when present, is believed to have been coincidental rather than a causative factor in most instances. The mean ages at onset for these two latter groups were about 70 and 59 years, respectively; however, there was appreciable overlap in the ages at onset.

The average age at onset recorded for the Rochester patients was about 67 years (about 10 to 15 years later on the average than reported in recent clinical series). This is believed to be a reflection in part of the decreasing incidence of postencephalitic cases in recent years. However, the Rochester study is believed to be far more representative of the illness of the population of the community as a whole than are series of clinical or specialists' cases which are believed to be biased in favor of younger patients.

For the Rochester cases, there was no appreciable difference by sex in the ages at onset; the incidence and prevalence rates were only slightly greater for males than for females. The age-specific incidence, prevalence and mortality rates were almost nil before age 50 years, rose gradually to age 60 years and increased sharply after 60 years of age.

On the basis of available data, about 2.5 per cent of the population may be expected to develop parkinsonism at some time during life. At any one time, the number of clinically identifiable cases is about 1.8 per 1,000 total population and nearly 1 per cent for the population aged 50 years and over. For the United States as a whole, it is estimated that there are at the present time about 266,000 clinically identifiable cases (95 per cent confidence interval 190,000 to 342,000 cases), making it one of the more serious neurologic disorders with which the population is faced. In view of the increasing life span of the population, it is likely that parkinsonism will become an increasingly serious problem unless some preventive measures are found.

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*If it can be assumed that the United States is randomly represented by the Rochester data, there are 19 chances in 20 (95 per cent confidence interval) that the annual diagnostic incidence rate for parkinsonism would be between 14.9 and 25.1 per 100,000 population and that between 25,000 and 43,000 patients could be newly diagnosed (and presumably at least this number are newly affected) each year.

On the basis of the limited data available, it appears that death rates among patients with parkinsonism are about one-third greater than the death rates from all causes among the normal population of the same age distribution.

A review of the case histories of the Rochester, Minnesota, patients revealed that in at least 16 per cent of the "idiopathic" cases, history of a similar illness in an immediate member of the family was recorded. Mjones[53] in Sweden personally interviewed a large series of patients and obtained positive family histories in 41 per cent of his idiopathic cases, 42 per cent of the encephalitic cases, and 19 per cent of the "arteriosclerotic" cases. (Family histories were considered least reliable in the last group.) Mjones, and also Allan[53,54] in the United States compiled striking series of pedigrees in which parkinsonism was noted in members of several generations and in which the trait behaved as a dominant characteristic with incomplete penetrance.

Denny-Brown[55] has suggested that idiopathic parkinsonism may be due to a chronic metabolic defect, and it is believed on the basis of the data reviewed here that this is likely to be of a genetic nature.

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## SUBACUTE COMBINED DEGENERATION OF THE CORD

The prevalence rate for pernicious anemia has probably increased in recent decades with the successful treatment of early cases. The prevalence of combined system disease probably parallels that of pernicious anemia.

On the basis of Mosbech's[56] recent monograph and the work which he reviews, pernicious anemia appears to have a high familial occurrence (30 per cent in families with adequate histories, 13 per cent in families with incomplete histories). There is a strong possibility that pernicious anemia, subacute combined degeneration of the cord, and gastric cancer associated with pernicious anemia develop as a result of a significant genetic influence. The specific mucopolysaccharide which is responsible for type A blood and which is also present in the gastric secretion is apparently present in a higher proportion of patients with pernicious anemia than in the general population.[57]

I am not acquainted with any population statistics on combined system disease. During the 10 years covered in the Rochester study, 17 local residents were observed with this diagnosis. In 14 (6 males, 8 females), the disorder was associated with pernicious anemia. The other 3 patients were males in whom the diagnosis of anemia was not made.

Eight of the 14 patients with pernicious anemia and 2 of the 3 patients without pernicious anemia noted onset of their symptoms during the 10-year period. (Incidence rate 3.3 per 100,000 per year.) On prevalence day, 8 of the pernicious anemia patients were still living in the community (prevalence rate 26.4 per 100,000 per year); none of those without pernicious anemia had survived to prevalence day. In only 2 of the patients was there a history of pernicious anemia in the family; this should be considered a minimal familial incidence for this series. All the cases of pernicious anemia occurred insidiously. In 1 patient, a blood picture of pernicious anemia with subacute combined degeneration developed 3 years after a total gastrectomy for a gastric ulcer.

In those patients with a blood picture of pernicious anemia, age at onset averaged 60 years, and age at time of the first diagnosis averaged 62 years. There was little difference by sex in the age at onset. The patients without pernicious anemia were 64, 67, and 69 years of age at the time of diagnosis.

On prevalence day, 8 of the patients with pernicious anemia were alive; the average age of the group was 71 years (range 60 to 80 years).

### INTRACRANIAL AND INTRASPINAL NEOPLASMS

Most statistics on brain tumors have been derived from a series of hospital admissions, the experience of neurosurgeons, or necropsy data. Suspected brain-tumor patients are selectively referred to large medical centers where facilities for neurosurgery are available, so that the hospital series are not necessarily representative of the general population. The tumor series of a neurosurgeon will be weighted in favor of operable cases and may also reflect the surgeon's known interest in particular types of tumors, such as pituitary tumors in the series of Cushing. Necropsy series are weighted in favor of noncurable disease and diagnostic problems and omit surgically amenable tumors such as certain meningiomas and intraspinal tumors.

There have been several population surveys[58] for cancer; these include brain tumors. The statistics from these surveys have been compared with the data from the Rochester neurologic survey.[9]

TABLE IV. INTRACRANIAL AND INTRASPINAL NEOPLASMS AMONG ROCHESTER, MINNESOTA, RESIDENTS 1945–1954, INCLUSIVE

| | NUMBER | PER CENT |
|---|---|---|
| Primary intracranial | 27 | 45 |
| Primary pituitary | 7 | 12 |
| Primary intraspinal | 8 | 13 |
| Metastatic (intracranial or intraspinal) | 18 | 30 |
| Total | 60 | 100 |

In the Rochester study, 60 cases of intracranial or intraspinal tumors were diagnosed among residents during the 10-year period (Table IV). Although primary lesions of the central nervous system comprise most of this series, the metastatic group is believed to be relatively underreported. In other series as well as in this one the metastatic sites are recorded irregularly as distinct diagnoses on the charts of patients with advanced, disseminated malignant disease. On the basis of age-adjusted rates from the Rochester data, an estimated 29,000 new cases of neoplasms affecting the central nervous system occur each year in the United States population; of these, 16,000 are primary intracranial (gliomas, meningiomas, and pituitary tumors) and about 4,200 are primary intraspinal lesions.

During the period of the Rochester study about 1 per cent of the 2,100 recorded deaths in the resident population were due to primary intracranial

neoplasms, and about 1.8 per cent of all deaths were due to primary and metastatic intracranial and intraspinal neoplasms combined. Only one death occurred among the patients with primary intraspinal tumors—surgery was generally more successful in preserving life in that group of patients than in patients with intracranial tumors.

The proportion of deaths due to brain neoplasms in Rochester is about twice that reported in the official mortality statistics. However, the excellent diagnostic facilities available to the community residents and a high necropsy rate in this population (67 per cent of all deaths) leads one to assume that the Rochester mortality statistics are closer to the true rates than are the figures obtained from national mortality statistics.

A breakdown of the primary tumors in this series according to histologic type has been presented elsewhere[9] but the small series does not warrant further consideration here. The age-specific incidence rate for primary brain tumors in Rochester increases in old age in contrast to the experience of other sources which show a diminishing rate after 55 years of age. This is explained in part by the detailed neurologic studies available for all persons in the community suspected of having neurologic disease. In addition, a few elderly patients believed to have died of cerebrovascular disease were found at necropsy to have primary intracranial tumors. None of the tumors in this series represented asymptomatic (neurologic) disease discovered at necropsy.

The material from Rochester was compared with several recent cancer morbidity surveys in United States communities. Slightly higher frequency rates were obtained in the Rochester survey than in the other community cancer surveys.[58] This is probably due to the more complete method of case collection in Rochester rather than to any geographic difference in the frequency of primary brain and cord neoplasms.

No genetic evaluation of the material from the Rochester study was made. Hauge and Harvald[60] recently presented a genetic study of the occurrence of intracranial tumors in near relatives of 535 patients with selected types of neoplasms and in family members of a control group of 249 patients. They concluded that: "Hereditary factors play scarcely any part in the etiology of gliomata, medulloblastomata and meningiomata, and similarly, these tumor forms do not seem to have any genetic relation to malignant growths localized elsewhere."[59] The importance of genetic mechanisms in the incidence of certain tumors associated with von Recklinghausen's disease, tuberous sclerosis, and certain vascular malformations is well recognized; however, the paper by Hauge and Harvald provides new information about a large group of primary brain tumors where genetic factors were largely unexplored. If genetic factors play no important role in the development of brain tumors, does this mean that the causes are purely exogenous? The problems relative to the elucidation of the complex etiology of brain tumors is similar to that of other malignant tumors.[60,61]

Additional epidemiologic and genetic studies of brain tumors are merited in the light of the numerical importance of the problem and our current paucity of knowledge concerning etiology.

SYRINGOMYELIA AND SYRINGOBULBIA

No incidence or prevalence figures for this condition were found in the literature. The relative prevalence suggested by Merritt[62] indicates that it is one of the less common diseases of the neuraxis. Merritt indicated that there is no difference by sex and that although patients may be seen at any age, most develop symptoms in the third and fourth decades.

In the Rochester population, there was only one patient, a woman 31 years of age at the onset of symptoms in 1928. In 1935, a syringomyelia cyst, extending from the upper cervical to the bulbar region, was drained. For several years her condition remained stationary. There was later progression; she was still alive on prevalence day. (Prevalence 3.3 per 100,000 population.)

TIC DOULOUREUX

Tic douloureux is one of the most common neuralgias observed by neurologists. It usually develops in middle or late life and is observed more frequently in females.[62] Although many clinical series have been reported, the Rochester study is believed to be the first attempt to obtain incidence and prevalence rates.

There were 28 cases in which this diagnosis was considered, but 9 of these were finally diagnosed as atypical face pain because the distribution of the pain did not conform to any division of the trigeminal nerve, or the pain was related to irritation of the teeth, mouth, or throat. Only one of the 9 patients with atypical pain was a male; 8 of the 19 with tic were males.

For the group with tic, there was no appreciable difference by sex for the characteristics reported below. The age of onset varied widely; the youngest patient was 28 years, the oldest 93 years. Most of the patients were in their sixth and seventh decades of life, and the mean age at onset for the entire group was 58 years.

Thirteen of the 19 noted onset while residing in the city during the 10-year period; 3 noted onset prior to 1945, and 3 with symptoms migrated to Rochester during the study period. The average annual incidence rate, based on 13 cases, is 4.3 per 100,000 population per year (Table II).

Age adjustment decreases the incidence rate slightly since a higher proportion of the Rochester, Minnesota, population are aged 40 years and over than in the total United States population.

On the basis of 4 new cases per 100,000 population per year there are in the United States approximately 7,000 new cases each year.

In the 19 Rochester cases there was no obvious correlation between sex and age and the location of the pain. Five patients had involvement on the left, 13 on the right, and 1 bilaterally. In 6, a single division of the nerve was affected; in the others, 2 or 3 divisions were involved.

The status of the 19 patients during the time they were observed is of particular interest. It is necessary to bear in mind that these patients are probably a representative sample of the illness and not merely a group of refractory patients who might be referred to neurologists or neurosurgeons.

Eleven of the 19 (58 per cent) had complete spontaneous recoveries, or only rare or mild attacks, within a few months after onset. Three of the 19 required one or more injections of alcohol into the division of the nerve involved, and 4 of the 19 had either sectioning of the sensory root or decompression of the nerve root and the Gasserian ganglion. One other patient had severe recurrences of pain for several years, but had not had alcohol injection or surgical treatment of the nerve.

The spontaneous remission rate of over 50 per cent observed here is important to consider when evaluating trials of new drugs without controls. Fields and Hoff[63] reported a series of 13 patients treated with large intramuscular doses of vitamin $B_{12}$ with "prompt and complete remission" in 9 patients which had not had previous surgical therapy and slower but "remarkable" relief in the other 4 patients who had had previous surgical treatment or nerve block. Although the comparability of the Rochester patients with the $B_{12}$-treated patients is not easily assessible, the high rate of spontaneous remissions in the Rochester resident patients raises some question as to the cause-and-effect relationship of the remissions in those receiving vitamin $B_{12}$. The same may be true for the small series of patients who were said to respond to treatment with Dilantin.[64]

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MYASTHENIA GRAVIS

Estimates of the number of affected persons in the United States have ranged from 1,500[65] up to 75,000[66]. This represents a fifty-fold difference of opinions. Data from several other sources suggest that a reasonable estimate lies between these extremes.

The Rochester survey disclosed only one diagnosed case suitable for a prevalence figure. One other patient was observed with an atypical course and was classified as "suspect" only. A prevalence rate of 3.3 per 100,000 population based upon the finding of a single patient is subject to considerable chance variation (Table III).

Preliminary data from a community survey of neurologic diseases in Charleston County, South Carolina (population, 190,000) provides a minimal prevalence rate of 2.6 per 100,000 based on 12 reported resident patients of whom 5 were living and identified on prevalence day.[67] Garland and Clark[68] arrived at the same minimal prevalence rate of 2.6 per 100,000 based on their survey in Leeds, England. If we assume an even geographic distribution of myasthenia gravis in the United States, the number based on the Rochester and Charleston results would be about 5,600 clinically identifiable cases. The 95 per cent confidence interval based on these data would be from about 2,000 to 10,000 cases.

In Charleston County, Alter[67] found a preponderance of females and similar rates for whites and Negroes.

Mortality rates for myasthenia gravis in Canada, in 1950, and in the United States over several recent years (1950 through 1954), based on the underlying causes of death, have averaged 1.3 per million population. The yearly rates were slightly higher for females than for males. A review of the Canadian mortality statistics, for 1951, showed that the rate based on death certificates coded to either underlying or contributing causes of death was 2.2 deaths per million popu-

lation. The rate of 2.2 deaths per million population per year may be used to arrive at a prevalence estimate for myasthenia gravis in the United States. This calculation involves the assumptions that myasthenia gravis is a fatal disease, that the diagnosis will appear on the death certificates of deceased patients, and that the median life expectancy for this disease is known. There are no suitable duration estimates available for an unselected case series, but for this exercise 10 or 20 years may be used.

The calculation assumes 100 per cent accuracy of diagnosis and reporting on the death certificates. In the Charleston study, Alter noted that for only 2 of 5 deceased patients with myasthenia gravis was myasthenia gravis reported on the death certificate. If one therefore assumes that one-half of the cases are reported on the death certificates, the estimated prevalence would be about 2.2 per million $\times$ 170,000,000 $\times$ 10 years $\times$ 2 (underreporting on death certificates) or 6,800 cases. If duration averaged as long as 20 years the number would be 13,600.

The prevalence rates from the Rochester and Charleston community surveys provide a minimal prevalence rate of about 3 per 100,000. By applying this to the total United States population, we are making the assumption that there is no significant geographic variation in incidence or duration of the disease in this population. There is no available evidence to date that would support or contradict that assumption. Because the prevalence of 3 per 100,0000 might be thought of as a minimal estimate and the problem of early diagnosis is well recognized, it would seem reasonable to suggest that there are perhaps 6,000 to 12,000 clinically identifiable cases of myasthenia gravis in the United States at the present time.

Most of the significant clinical information that has accumulated concerning this disease has come from analyses of case series and is discussed elsewhere in this symposium. In several recent series,[69,70] the disease is reported to be more prevalent in females (about 60 per cent) and the age of onset lower in women than in men, with women predominating up to age 40 years and men predominating after that.

According to Metrakos,[71] myasthenia gravis in adults shows no obvious familial aggregation of cases. Congenital cases, which are transient, are sometimes observed in offspring of affected mothers. A true congenital type in the offspring of normal parents is very uncommon but may occur in siblings, perhaps as recessive trait.[71] Aside from the occurrence of thymoma and perhaps thyroid disease in patients and aside from the occasional, and perhaps coincidental, exacerbation of the disease with pregnancy, no associated condition or exogenous factor has been identified.

It would seem that, in view of the difficulty in early diagnosis and the apparent low incidence of this disorder, an attempt to clarify any of the basic population features of the disorder from community survey data is not likely to meet with much success. It seems reasonable to assume that eventual description of the pertinent pathologic mechanism will come from biochemical research in clinical series. The relative roles of heredity and environment as etiologic factors are still to be clarified and are also likely to come from studies of series of cases.

HEREDITARY MUSCULAR AND NEUROMUSCULAR DISORDERS

*Muscular Dystrophy.—*

*Population surveys:* There are several useful population reports in the literature. Herndon[72] surveyed many sources of medical and orthopedic information in the State of North Carolina and located 133 index cases and 6 other cases in their families in the population of about 3,500,000. He estimated that the minimal prevalence rate for North Carolina was about 4 cases per 100,000 population. Herndon felt that his data might be deficient for nonwhites and for persons under 16 years of age.

Walton and Nattrass[73] surveyed Northumberland and Durham Counties in England, and in population of about 2,262,000 found 84 cases of muscular dystrophy (a prevalence of about 4 cases per 100,000 population). Of these 84 cases, 48 were of the Duchenne type, 18 were of the facioscapulohumeral type, and 18 were of the limb-girdle type. In addition, they observed two cases of distal myopathy and 1 case of ocular myopathy.

The Duchenne type of muscular dystrophy is characterized by occurrence almost entirely in males and onset usually in the first 4 years of life but occasionally as late as the third decade. Its transmission is as a sex-linked recessive trait and the mutation rate is high ($1 \times 10^{-4}$ according to Tyler and Stephens).[74]

The characteristic features of the facioscapulohumeral form are a variable age of onset at any time from early childhood to late adult life in both sexes, with occurrence of abortive cases and transmission usually as an autosomal dominant gene. Tyler and Stephens[75] have reported 58 cases of this disorder occurring in 1,249 individuals in a single kindred. The disease in this kindred shows a typical mendelian dominant pattern of inheritance with complete penetrance and variable expressivity. Although most of the cases were benign, occasionally a severely handicapped patient was observed in this kindred. The disease, which appears to be comparatively common in parts of Utah, has been traced back to one of the early pioneers who was born in England in 1775, settled in the Salt Lake area in the early nineteenth century and reared a large family. Tyler and Stephens note that the disease progresses more rapidly if symptoms of dystrophy begin at an early age. They present the view that the severity of expression depends upon the environment and the over-all genotype of the individual concerned.

The limb-girdle form of disease occurs in either sex, has its onset usually within the first 3 decades but occasionally later and is usually transmitted as an autosomal recessive character.

In the Rochester, Minnesota, survey there were 4 diagnosed cases and one suspected case in the local population during the 10 years.

One of the 4 patients had the Duchenne type with pseudohypertrophy, and the other 3 had facioscapulohumeral disease. The boy with the Duchenne type of disease was 3 years of age at onset; he resided in Rochester at the time of onset and until he was 9 years of age, when his family moved out of the city.

The 3 patients with facioscapulohumeral disease were male; two of them brothers. Other cases were recognized in the families of these 3 patients. The ages at onset were 10, 30, and 44 years, respectively. Two of the patients were

residing in the community on prevalence day (prevalence rate about 6 per 100,000 population).

*Mortality studies:* Muscular dystrophy is included with amyotonia congenita and myotonia in rubric 744.1 of the *International List of Diseases and Causes of Death.* Ordinarily, the published rates are based on all deaths included in this rubric. In 1950 and in 1951, the death rates, based on the underlying cause of death, in the United States were 0.2 per 100,000 population. In Canada, in 1951, there were 20 deaths coded to rubric 744.1; 16 of these deaths were recorded as deaths from dystrophy and 4 as deaths from amyotonia congenita. In addition, muscular dystrophy was coded as a contributory cause of death in 7 instances. If the same ratio of deletions (amyotonia) and additions (cases coded as contributory causes of death) are applied to the United States deaths for 1950 and 1951, the annual death rate would remain about 0.2 per 100,000 population. The "corrected" rate for Canada is similar to that for the United States. After 1951, the official death rate in the United States increased to 0.3 per 100,000 population, but whether this reflects a real increase or some artifact in coding remains to be seen.

The data from Rochester, Minnesota, North Carolina, and England suggest that the prevalence for clinically identifiable muscular dystrophy is about 4 to 6 per 100,000 population. If the latter value is applied to the United States population, there would appear to be about 10,000 cases in the population at the present time. If the average duration of muscular dystrophy after onset were as long as 20 years and the present official death rate of 0.3 per 100,000 population were correct, the prevalence for clinically identifiable muscular dystrophy on this basis would be about 10,000 cases.

*Myotonic dystrophy:* Walton and Nattrass[73] in their survey of Northumberland and Durham Counties, England, found 15 cases (8 male and 7 female) for a prevalence rate of almost 1 per 100,000. The ages at onset ranged from childhood to 62 years, with a mean of about 30 years.

In Rochester, there was 1 patient who noted onset prior to the study period but who was still alive in the city on prevalence day. He had several affected siblings who were living elsewhere.

There are no adequate mortality statistics for this disorder. It is generally agreed that it occurs in both sexes and is transmitted in most instances as an autosomal dominant.

*Myotonia congenita (Thomsen's disease):* Thomsen[76] has shown that this disorder, which features myotonia without dystrophy, is inherited as an autosomal dominant trait and occurs to the same extent in both sexes. The large majority of the probands in Thomsen's material noted onset before age 12 years. Paramyotonia was generally reported in conjunction with these cases.

Recently Tyler[77] and Drager, Hammill, and Shy[77] reported the occurrence of paramyotonia as a dominant trait in a family in which myotonia congenita did not occur. Whether paramyotonia in the absence of myotonia congenita represents a distinct genetic trait as suggested by these investigations or whether there is a difference in expression of the trait in such families remains to be clarified.

Walton and Nattrass[73] in what they consider to be almost "complete ascertainment of the cases of myopathy in Northumberland and Durham" found 6 cases of myotonia congenita (1 male, 5 female) for a prevalence rate of 0.3 cases per 100,000 population. The ages at onset ranged from 9 through 24 years with a mean of 18 years.

One patient who moved to Rochester in 1950, when her husband became employed there, was noted to have myotonia during a routine pre-employment examination at the Mayo Clinic. Muscle stiffness had been present all her life; two of her siblings, living elsewhere, had also been affected. The one residing patient is responsible for a prevalence rate of 3.3 per 100,000 population, but a range of rates should be referred to here also.

*Infantile progressive muscular atrophy (Werdnig-Hoffmann's disease):* It is still not clear whether this disorder and amyotonia congenita (Oppenheim's disease) are identical.[62] Brandt,[79] in his survey in Denmark, collected data on 156 cases, of which almost half had been diagnosed previously as amyotonia congenita.

During the course of his 4-year study (1944-1948), Brandt[79] observed 28 new cases which is considered as a minimal incidence for Denmark for the period. The annual incidence rate based on these data is about 0.7 case per 100,000 population. Seventeen of the patients were still alive in 1948, so a minimal prevalence figure for Denmark is 0.4 per 100,000 population. There was no difference in the sex ratio in his material; in about 80 per cent the first clinical manifestations developed before one year of age. In those children for whom details were available, death occurred before the end of the first year of life in 56 per cent, in the age period 1 to 10 years in 33 per cent, and after 10 years of age in 11 per cent.

Brandt's probands were "found to be distributed equally over the entire of Denmark, just as their ancestors are scattered over the various countries of the country." No final conclusion concerning the role of heredity can be given, but Brandt's data, including parental consanguinity in 13 per cent of his patients, suggest that it is a recessive trait.

In Rochester, Minnesota, during the 10 years, there was one resident with Werdnig-Hoffmann's disease (average annual incidence for the 10 years was 0.3 per 100,000 population per year). The first clinical manifestation was at age 8 years on prevalence day. (Prevalence rate 3.3 per 100,000 population.)

In view of the confusion in diagnosis of amyotonia congenita and infantile progressive muscular atrophy, it is uncertain how valid mortality statistics will be. In Canada, in 1951, there were 4 deaths reported as due to infantile progressive muscular atrophy, and there were 9 deaths reported as due to amyotonia congenita. The death rates for all these cases combined would be almost 1 per 100,000 population per year. If one assumed accurate diagnosis and reporting and if, as in most fatal diseases, the annual mortality rate reflects the annual incidence rate, it would appear that the rates in Denmark and Canada are similar. No suitable death rates are available for the United States; the 95 per cent confidence limits for this disorder in Rochester encompass the rates for Denmark and Canada.

*Peroneal muscular atrophy (Charcot-Marie-Tooth):* This disease is characterized by distal muscular atrophy and sensory changes, particularly in the lower extremities and often in conjunction with a variety of lesions of the long tract and brain stem. Cases with this diagnosis have long been recognized as occurring in familial constellations. Tyler considers the usual mode of inheritance as single dominant and suggests that since variability in the clinical picture between pedigrees may be appreciable that each pedigree is the effect of a different mutation. He also has expressed the belief that the peroneal muscular atrophies form a continuum with the hereditary ataxias "and result from many probably mechanistically related but independent mutations."[77] According to Bell, the mode of inheritance may be dominant, autosomal recessive, or sex-linked recessive. The recessive cases have an earlier average age at onset than the dominant cases; and in Bell's series,[80] the mean age at onset was 19 years for dominant cases, 16 years for sex-linked cases, and 13 years for recessive cases. According to the study of 353 kindred by Bell, one parent was affected in 220 (62 per cent), both parents were normal in 83 (24 per cent), and in 50 (14 per cent) the pedigree was compatible with a sex-linked mode of inheritance.

Since there is a preponderance of males in the sex-linked group and in the recessive cases of Bell,[80] the over-all sex ratio shows a preponderance of males, even though the dominant form which is most often seen shows no selectivity for either sex.

The most detailed population estimates for this disorder have come from the North Carolina survey by Herndon.[72] He found 61 index cases and 126 additional living patients in the families of the index cases. The minimal prevalence rate based on these cases was 5.4 per 100,000 population and the estimated number in the United States, assuming an even geographic distribution, is at least 9,000.

In the Rochester survey, no local case with this diagnosis was observed, whereas in the Guam population of the same size three cases (2 in 1 family) were observed in a recent survey.[81] As explained earlier, if the illness were randomly distributed and 3 cases were located in a sample of 30,000 population, the true rate would be likely to fall between 2.3 and 29.2 per 100,000 population, and the experience in Rochester could well occur by chance. Because of the problem of assessing relatively uncommon hereditary disorders in a small population, the experience in the North Carolina survey seems to offer the best available prevalence estimate.

It is of interest that Herndon found peroneal muscular atrophy to be more prevalent than progressive muscular dystrophy. Since life expectancy is much greater for peroneal muscular atrophy, it is likely that the annual incidence of dystrophy with its shorter duration is greater than that of peroneal atrophy.

A comparison of Herndon's survey results of muscular dystrophy and for peroneal muscular atrophy in North Carolina may provide further information about the relative frequency of different types of these illnesses in the population. In addition to 133 index cases of dystrophy, he learned of 40 secondary cases (ratio of 0.3 secondary to each index case); as to peroneal muscular atrophy, there were 172 secondary cases for 61 index cases (ratio of 2.8 secondary to each index case). This suggests that a higher proportion of dystrophy cases were of

the recessive type and also that in North Carolina an appreciable number of the patients with peroneal muscular atrophy were not under medical supervision. The latter finding may be due to the variability of expression of this disease and to the fact that a large percentage of affected persons are perhaps not appreciably handicapped. Furthermore, the ratio of living secondary to total secondary cases was 6 of 40 (15 per cent) for dystrophy and 126 of 172 (73 per cent) for peroneal muscular atrophy. The life expectancy of the recessive type of dystrophy, which appears to occur more often than the dominant form of dystrophy,[73] is known to be relatively short. In contrast to this, the life expectancy in peroneal muscular atrophy is considerably longer.

OTHER HEREDITARY DISEASES

*Huntington's Chorea.*—Huntington's chorea is recognized as a dominant hereditary disease of the basal ganglia and cerebral cortex characterized by onset in adult life of chorea and mental deterioration.

In the Rochester, Minnesota, population there were 2 patients: one of these with a recent onset, who was at home; the other, her brother, was institutionalized. On the basis of the diagnosed cases, the rate in Rochester was 6.7 per 100,000 population. The earlier discussion on rare hereditary diseases and small samples is pertinent here. In spite of the expected fluctuation in rates, with the concentration on dearth of affected families in small populations, the population statistics, which have been published on this subject, are surprisingly similar. Brothers and Meadows[82] found 57 living patients in Victoria, Australia (prevalence 2.3 per 100,000 population); Bickford and Ellison[83] found 19 cases in Cornwall, England (prevalence 5.6 per 100,000 population—considered a minimal rate); Pleydell[84] reported 13 cases in Northamptonshire for a prevalence rate of 4.9 per 100,000 population; and Pearson and associates[85] found the prevalence rate to be 5.4 cases per 100,000 population in Minnesota.

There were 26 deaths reported as Huntington's chorea in the 1951 Canadian mortality statistics. The average annual mortality rate and the minimal incidence rate based on these data are each 1.9 per million population. If reporting were complete and if the average duration after the onset of symptoms were 20 years, the prevalence rate per 100,000 population would be 3.8; if the duration were 15 years, the prevalence rate per 100,000 population would be 2.9.

Since the illness is an autosomal dominant trait with high penetrance, it occurs in both sexes and may be transmitted by either sex. The age at onset varies and is thought to be fairly constant in some families, but most cases occur between 25 and 50 years of age. The mean ages reported are 38 years (Brothers and Meadows), 35.5 years (Bell),[85] 43 years (Bickford and Ellison),[83] and 38 years (Davenport).[87]

Some authors still claim that anticipation (a tendency to earlier onset in succeeding generations) may occur in this disorder. The general concept of anticipation is discounted by most geneticists, particularly where a disease may have a wide range of expression (in terms of severity, rapidity of progression, and age at onset). This variability in expression is probably the significant factor in situations suggesting anticipation, since the reverse type of variation is pre-

vented by the nature of the disease which precludes procreation in very early and severe cases.

Bell[86] found the average duration of this disease in 204 cases, with termination at death, to be 13.7 years. Brothers and Meadows[82] found a similar figure of 13 years for 36 cases in which the ages at onset and death were both known. These latter figures might be too small, for some long-lived patients in their series would still be alive and would not enter into the calculations of average duration. Life table computations provide a more accurate measure of life expectancy for this type of disorder.

*Tuberous Sclerosis.*—Tuberous sclerosis, also known as epiloia and by its cutaneous manifestation as adenoma sebaceum, is only occasionally seen in its full extent with mental defect, epilepsy, and intracerebral and other tumors. It is manifested in either sex, and, usually, early in childhood, when the skin lesions or cerebral symptoms develop. It is transmitted by either sex as an irregular dominant characteristic which may show variable degrees of expression.[88]

The disorder has been well described in Caucasians and, recently, in an African Bantu family[89]. It is likely that the disorder, which Penrose estimates has a mutation rate of 1:40,000,[90] occurs in all races.

This diagnosis was made in one Rochester resident patient, who was examined at the Mayo Clinic at the age of two years following the onset of generalized convulsions. A diagnosis of tuberous sclerosis (epiloia) was made with the aid of roentgenogram of the skull, which showed calcified areas in the left parietal region. Skin lesions suggestive of adenoma sebaceum were noted. The child had increasingly severe convulsive episodes and was severely retarded mentally. He was three years of age and still living in Rochester on prevalence day (prevalence 3.3 per 100,000 population).

*Hepatolenticular Degeneration (Wilson's Disease) and The Hereditary Spinal and Cerebellar Ataxias.*—There were no cases with these diagnoses among local residents in the Rochester population during the 10 years of the study. Problems relating to small samples, particularly of the uncommon hereditary disorders, have already been discussed. When no cases are found in a population of 30,000 in a 10-year period, the 95 per cent confidence interval falls between 0.0 and 1.2 per 100,000 population for average annual incidence and between 0.0 and 3.7 per 100,000 population for prevalence.

*Hepatolenticular degeneration (Wilson's disease):* This metabolic dysfunction, in which serum ceruloplasmin is reduced, and excretions of amino acid and copper are altered, is inherited as a recessive trait. The disease, when fully manifested, is characterized by cirrhosis of the liver, tremor, muscular rigidity, and other symptoms of degeneration of the basal ganglia and cerebral cortex and the characteristic yellow-brown Kayser-Fleischer ring at the corneal margin.[91] A *forme fruste*, in which dysfunction of basal ganglia may not be evident, may exist as an idiopathic cirrhosis in children and young adults.[92] Data on the incidence in the population and on the mutation rate have not come to my attention. The mortality rate for Canada in 1951 was 0.3 per million population. The disease is well recognized in Japan, Europe, and the United States.

*The hereditary ataxias:* No population survey data on this subject have come to my attention; the absence of any cases in the Rochester study suggests that the disease is uncommon and that the prevalence rate may range from just above zero to about 3.7 per 100,000 population.

Data on the incidence in the population and on mutation rates for diseases in this category have not come to my attention. The mortality rate for Canada in 1951, based on 5 deaths due to this cause, was 0.3 per million population; this should be considered as a minimal value.

The hereditary ataxias represent a complex grouping of neurologic disorders. From Greenfield's[93] description one may conclude that a variety of isolated degenerative lesions or combinations of lesions may develop and affect the cerebellum, the long tracts, nerve cells and nerve roots of the spinal cord, the optic nerves and cerebrum, and other neuronal tissue. In some families, the lesions and clinical symptoms in different affected members are similar; in other families the clinical picture and distribution of diseases varies "tending to show that genetic and/or environmental modification is important."[94] Still, it seems that each ataxic family may have its own peculiar combination of signs and symptoms which distinguish it from other ataxic families and which Schut[94] succinctly called "the biotype" of each family.

It would seem that the hereditary ataxias comprise an appreciable segment of a hypothetical continuum of hereditary neurologic disorders, for according to Greenfield[93] this group of disorders is "linked to paralysis agitans on the one hand . . . . . and to amyotrophic lateral sclerosis on the other." According to Tyler[77] the link can be extended to include the peroneal muscle atrophies as well.

On clinical, pathologic, and genetic grounds, the most striking feature of the ataxias is the variability of manifestations. There are all gradations between pure cerebellar, mixed cerebellar and brain stem, and spinal syndromes depicted by simple modes of inheritance. A descriptive summary, based on the characteristic clinical features, is given by Merritt,[62] and Greenfield[93] has attempted a classification based on pathologic material. Schut,[94] combining the genetic, clinical, and pathologic features of the ataxias, derived a classification which, although lengthy, gives a good picture of the interplay of the three underlying components. Under the main headings of recessive, dominant and sex-linked, or recessive and atypical inheritance, he lists the major types and variations of the ataxias along with the ages of onset, clinical symptoms, pathologic findings, and associated conditions.

For descriptive purposes, it is perhaps convenient to group the ataxias into three major types or varieties: those depending upon involvement of the posterior columns (Friedreich's ataxia), the cerebellum and its pathways (cerebellar ataxia), and the pyramidal system (spastic paraplegia). The age at onset in the first group is about 12 years and almost always less than 20. The mode of inheritance is usually recessive, although a few dominant pedigrees have been described. About 10 per cent of patients have parents who are first cousins. In the second group, the age at onset is significantly higher than that of the first group, usually between 26 and 30 years. The mode of inheritance is domi-

nant, with some irregularity of manifestation. The third group appears at an early age and is usually recognized by the age of 2 or 3 years.

Little information is available on the nature of the biochemical lesions that may be responsible for the hereditary ataxias.

INFECTIOUS DISEASES

*Herpes Zoster.*—Only one previously published population survey for herpes zoster has come to my attention and that was made by Seiler[95] in Edinburgh, Scotland. During a period of 18 months in 1947-1948, some of the physicians and a few of the hospitals provided Seiler with special reports on 246 patients. It is uncertain how he obtained incidence rates from these data, but he estimated that he had about 20 per cent ascertainment of the local cases and concluded that the average annual incidence was about 200 per 100,000 population. Although there were more females than males in his sample, he reported no significant difference in the attack rates by sex. Three of the 184 patients whom he personally queried described a contact with chickenpox. He concluded that since there was no correlation of the monthly incidence of herpes zoster in his sample and the monthly incidence of chickenpox in the local schools, no close association of zoster and chickenpox could be established.

In the Rochester series, 158 women and 90 men were affected. The average annual incidence rates are 94 per 100,000 population for women and 69 per 100,000 population for men (Table V). The magnitude of this difference suggests that there may well be a true difference in incidence rates by sex. Information from other sources on this point has been contradictory, and further investigation is merited before any conclusions are drawn. The over-all age-specific incidence rates increase markedly beyond middle life. An analysis of incidence rates by age and sex groups showed that the most marked disparity by sex was in the 55- to 69-year age group. The peak incidence of the cases in Rochester occurred in the fall and spring, and although the seasonal difference is not a statistically significant one, it is similar to that reported by Allen[96] and by Seiler.[95] The number of cases each year was fairly stable except in 1949, when the number was nearly double the average, and in 1952 and 1954, when it was about two-thirds of the average.

TABLE V. INCIDENCE OF HERPES ZOSTER BY AGE AND SEX, ROCHESTER, MINNESOTA, RESIDENT POPULATION, 1945-1954, INCLUSIVE

| AGE GROUP IN YEARS | NUMBER OCCURRING IN 10 YEARS BOTH SEXES | AVERAGE ANNUAL INCIDENCE/100,000 POPULATION | | |
|---|---|---|---|---|
| | | BOTH SEXES | MALE | FEMALE |
| 0–14 | 9 | 14 | 15 | 12 |
| 15–34 | 58 | 60 | 50 | 67 |
| 35–54 | 61 | 80 | 72 | 86 |
| 55–69 | 76 | 186 | 145 | 218 |
| 70 plus | 44 | 242 | 224 | 254 |
| Total | 248 | 83 | 69 | 94 |

In the records of 4 of the Rochester patients there was some reference to exposure to chickenpox. Because of inadequate data on the number of cases of chickenpox in the community, no attempt was made to correlate the incidence for herpes zoster with that for chickenpox. In one instance in the Rochester series, a husband and wife developed herpes zoster within 2 days of each other.

The involved dermatome was described in almost all patients (Table VI). The ophthalmic division of the trigeminal nerve was affected more often in males and the cervical dermatome more often in females, but the differences are not statistically significant by sex for any level.

In 3.2 per cent of the Rochester cases, there was evidence that the attack of herpes zoster represented a recurrence of the disease; in Seiler's study[94] a history of prior attacks of herpes zoster was obtained in 3.3 per cent of his cases.

TABLE VI. HERPES ZOSTER INFECTION—LOCALIZATION BY DERMATOME IN ROCHESTER, MINNESOTA, RESIDENT POPULATION 1945-1954, INCLUSIVE

| LOCATION | NUMBER IN 10 YEARS | PER CENT | | |
|---|---|---|---|---|
| | | BOTH SEXES | MALE | FEMALE |
| Cr $V_1$ | 23 | 9 | 17 | 5 |
| Cr $V_2$ or $V_3$ | 6 | 2 | 2* | 3 |
| Cr IX | 2 | 1 | 0 | 1 |
| C | 28 | 11 | 7 | 14 |
| T | 139 | 56 | 53 | 58 |
| L | 37 | 15 | 17 | 14 |
| S | 10 | 4 | 4 | 4 |
| Not Specified | 3 | 1 | 0 | 2 |
| Total | 248 | 99 | 100 | 101 |

*One with Ramsay Hunt syndrome; one with localization to Cr IX and Cr$V_1$ and $V_2$.

In 10 women (3 aged 35 to 54 years, 4 aged 55 to 69 years, and 3 aged 70 years or over) and in 3 men (all aged 70 years or over) with herpes zoster, there was concurrent malignant disease (women: breast 3, cervix 2, sigmoid colon 2, and bladder, parotid gland, and skin 1 each; men: lung, lips, and skin 1 each). If the age-specific cancer prevalence rates for the white population of the United States[58] are applied to the number of herpes zoster patients in Rochester, an "expected" prevalence of only 2.6 cases of cancer is found. The difference between 13 and 2.6 among 248 cases is a statistically significant one and suggests an association of cancer and herpes zoster in some cases. It also suggests that in the presence of herpes zoster, a careful search for a malignant lesion is indicated.

In 4 instances of involvement of the first division of the trigeminal nerve there were ophthalmic complications. These included two cases of keratitis and two cases of uveitis and secondary glaucoma.

Postherpetic neuralgia has been recognized as a sequela of herpes zoster, particularly in elderly patients. In Rochester, 18 of the 248 patients were observed at the clinic for pain which persisted 4 weeks or more after the onset

of the herpes zoster. The age and sex distributions are shown in Table VII. The rates increase with age; the incidences by sex are not statistically significant.

*Neuronitis* (*Landry-Guillain-Barré Syndrome*).—No reports of specific studies on the incidence and prevalence of this disease were found. Merritt[62] states that of the polyneuritides it is second to alcoholic polyneuritis in frequency and that it occurs in both sexes equally at almost any age but is especially prevalent in the third or fourth decades.

In Rochester, 3 cases (2 male, 1 female) developed in a sporadic fashion during the 10 years. The ages at onset were 48 and 54 years for the men and 44 years for the woman. All were observed at the Mayo Clinic shortly after the onset of symptoms, at which time the diagnosis of neuronitis was made. On examination of spinal fluid, the protein was increased and the cell count was low in all 3 patients. Although all made satisfactory recoveries from their acute illness, they had some slight to moderate residual muscle weakness which lasted for several months. No specific etiologic agent was identified in these cases.

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TABLE VII. POSTHERPETIC NEURALGIA IN ROCHESTER, MINNESOTA, PATIENTS 1945-1954, INCLUSIVE

| AGE | MALES | | | FEMALES | | |
|---|---|---|---|---|---|---|
| | NUMBER AFFECTED | POSTHERPETIC NEURALGIA | | NUMBER AFFECTED | POSTHERPETIC NEURALGIA | |
| | | NUMBER | PER CENT | | NUMBER | PER CENT |
| 0–14 | 5 | 0 | 0 | 4 | 0 | 0 |
| 15–34 | 19 | 1 | 5 | 39 | 0 | 0 |
| 35–54 | 24 | 1 | 4 | 37 | 0 | 0 |
| 55–69 | 26 | 2 | 8 | 50 | 6 | 12 |
| 70+ | 16 | 4 | 25 | 28 | 4 | 14 |
| Total | 90 | 8 | 8.9 | 158 | 10 | 6.3 |

## COMMENT

Data for a variety of disorders touching on several aspects of neurology have been presented. The discussion for each of the subjects covered in the paper has been oriented toward the use of the available statistical and genetic data to provide some foundation for further clinical, laboratory, or definitive type epidemiologic research. The available data also may be helpful in realistic planning for professional and medical care facilities required by the population and for the most promising use of some of our research resources.

The availability of information on incidence and prevalence data facilitates the recognition of unusual situations when they do arise, but data of sufficient reliability are still not generally available for many of the disorders affecting the nervous system. An example of the use of data still in short supply might be cited. It is conceivable that if base-line incidence rates for grand mal epilepsy in infants had been available in 1952 the association of an increasing incidence

of seizures with the use of vitamin $B_6$-deficient SMA formula then available might have been recognized sooner and thus prevented numerous cases that occurred during the next 2 years.

By the same token, base-line data are needed if research workers are to recognize incidental coexistence of one illness with another illness or with some other circumstance. An example of this which was recently presented[8] relates to the 2 per cent of elderly patients with diabetes who also had parkinsonism. The information available now suggests that this could be coincidental rather than a cause-and-effect relationship.

Population survey results, which comprise most of this report, occasionally disclose an unusual concentration or a dearth of cases in a broad geographic region or in a population "isolate." If these circumstances are not due to chance, their explanation in terms of the natural history of disease may be of considerable significance, as they affect research and therapy for the specific disease itself and for numerous other obscure diseases of the nervous system. Examples of phenomenal situations which have recently come to the attention of neurologists and are under epidemiologic investigation include "Kuru" in Australian New Guinea;[97] Minamata disease in Kyushu, Japan[98]; and amyotrophic lateral sclerosis in the Mariana Islands of the Pacific.[48,50,51]

SUMMARY

The results of the analysis of data for selected neurologic diseases from surveys and from several sources of mortality data were reviewed.

The results of a survey in the population of Rochester, Minnesota, were presented in some detail, and the data from this source and others which are available were used in many instances to obtain estimates of incidence and prevalence for the population of the United States. The uses of such estimates for base-line comparative studies and for matters pertaining to medical care and research resources were considered.

The interrelationship of genetics and epidemiology was discussed and examples of the combined effect of exogenous and hereditary factors in the causation of disease have been presented. The concept of a continuum of hereditary diseases of the nervous system was reiterated, and the need for elucidation of the biochemical nature of the genetic lesions was illustrated.

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# CEREBROVASCULAR DISEASES: PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

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THE last 10 years have witnessed a resurgence of interest in vascular disturbances of the brain, and the "stroke" has become the subject of methodical study. Our knowledge of its pathologic anatomy has been broadened, and therapeutic progress of a practical kind has been achieved. A brief review of some of these advances, by indicating the trend of new ideas, may not be out of place as an introduction to a discussion of the pathophysiology, diagnosis, and treatment of these diseases.

First and foremost, the use of anticoagulant drugs for the *prevention* of transient ischemic attacks and the *prevention* of full-blown cerebral thrombosis has resulted in a marked refinement of diagnostic precepts within the field of strokes and indeed within the general field of "cerebral attacks" of all kinds. For the clinician, the price of anticoagulant therapy is a precise diagnosis. The high incidence of occlusion of the internal carotid artery in the neck has been demonstrated, and the great frequency of disease in the vertebral-basilar system has become plain. New light has been shed on "attacks of cerebral vasospasm," and it has been amply shown that these episodes of transient cerebral ischemia are related to incipient cerebral thrombosis. Recent information on the behavior of embolic material in cerebral embolism has provided an explanation for the many cases of cerebral infarction in which no embolus could be found pathologically at the expected site. In all probability the embolus not infrequently fragments or undergoes lysis and disappears after precipitating local infarction. The intimate relationship of hemorrhagic infarction to embolism and of lacunar disease to the presence of hypertension has been demonstrated. The nitrous oxide method of measuring cerebral blood flow and cerebral metabolism has been a notable advance, and further useful information is being provided currently. The use of cerebral arteriography has increased the precision of diagnosis during life. A wealth of therapeutic measures have come and, for the most part, gone as early enthusiasm waned, e.g., nicotinic acid, papavarine, histamine, sympathetic stellate block, and carbon dioxide inhalations; however, anticoagu-

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lants are proving effective in the treatment of cerebral thrombosis. They constitute only a delaying action, an interim measure, and the real solution, of course, lies in the eradication or prevention of atherosclerosis and hypertension. Ruptured saccular aneurysm is slowly yielding to neurosurgical devices. These advances—and many others could be added—although not representing a major break-through, constitute a significant contribution to our understanding of this extremely important area of disease.

Meanwhile, the basic pathologic processes with which the clinician has to grapple have not changed appreciably. Cerebral thrombosis, cerebral embolism, hypertensive hemorrhage, and ruptured saccular aneurysm remain "The Big Four," and my remarks will be confined for the most part to them. Acute hypertensive encephalopathy, cerebral thrombophlebitis, and the arteritides complete the roster but are to be regarded as relative rarities.

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## PATHOPHYSIOLOGY

*Cerebral Thrombosis.*—This may result from: (1) atherosclerosis, (2) systemic hypotension, (3) trauma to the carotid artery, (4) arteritis (idiopathic giant cell arteritis of the aorta, periarteritis nodosa, temporal arteritis, meningovascular syphilis, meningitis, etc.), (5) complication of ruptured saccular aneurysm, (6) complication of arteriography, (7) hematologic disease (polycythemia, sickle cell disease, etc.), (8) migraine, (9) hypoxia, (10) dissecting aortic aneurysm, and (11) cerebral venous thrombosis.

Of this list only thrombosis with atherosclerosis is of any importance numerically in the causation of strokes; the others are included here only for the sake of completeness. Atherosclerosis in the cerebral arteries does not differ from, and roughly parallels in severity, that in arteries elsewhere in the body. Suggestions that in recent years atherosclerosis may be increasing in cerebral arteries out of proportion to that in other arteries are based on faulty selection of data. That atherosclerosis tends to be laid down at bifurcations, branchings, and curves is well exemplified in the case of the intracranial arteries portrayed in Fig. 1, where the location of the most severe atherosclerosis is diagrammatically shown. Since thrombosis occurs in relation to atherosclerotic plaques, it is at the sites of predilection illustrated that cerebral thrombosis is prone to occur. Clinically, thrombotic involvement is approximately as frequent in the vertebral-basilar system as in the carotid system. When hypertension is present, atherosclerosis is more severe and is laid down in the smaller surface vessels of the cerebrum and cerebellum and in the small penetrating branches which run to the basal ganglia and internal capsule from the middle cerebral artery, to the thalamus from the posterior cerebral arteries, and to the brain stem from the basilar artery. Occlusion of these penetrating vessels leads to small circumscribed infarcts several millimeters in diameter which in the healed stage leave behind a tiny trabeculated cavity termed a "lacune." Lacunes are probably the most common vascular lesion of the brain and are a hallmark of hypertension. Singly they may cause little or no permanent neurologic deficit, but when several are present they lead to pseudobulbar palsy (spasticity of gait, marche *à petit pas*, increased tendon

reflexes, slurred speech, dysphagia, spasms of laughing and crying, and impaired memory).

The mechanism by which thrombus becomes deposited on a plaque is ill understood. The timetable of thrombus formation is not known, and whether it takes hours or weeks to build up and occlude the lumen can only be surmized. In cerebral vessels it seems that the lumen must be greatly narrowed by atherosclerosis before thrombosis is superimposed. It is important to realize that the cerebral circulation tolerates plaques surprisingly well, and it is not uncommon to find at autopsy the most advanced atherosclerosis in a patient whose nervous

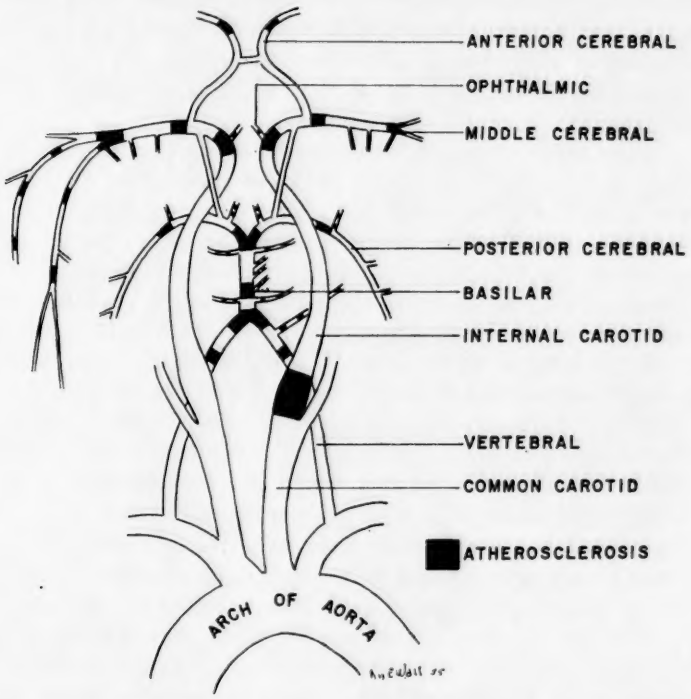


Fig. 1.—Diagram of cerebral arteries to show the sites of predilection for atherosclerotic deposition.

system was entirely intact clinically. Only when thrombosis is added are symptoms liable to appear—in other words the problem is a dual one, atherosclerosis plus thrombosis. Indeed, a propensity to intravascular thrombus formation could constitute a relatively graver threat than atherosclerosis, but at present there is no method of detecting hypercoagulability of the blood (if such an abnormality exists). Atherosclerotic narrowing of a vessel may by itself determine ischemia or infarction if the systemic blood pressure falls, in which case a previously asymptomatic reduction in the marginal reserve of blood flow becomes unmasked.

The immediate effect of a vascular occlusion is highly variable, depending on several factors, the most important of which is the availability of collateral

anastomotic blood flow. When the occlusion is pre-Willis, i.e., lies proximal to the circle of Willis in the common carotid, internal carotid, vertebral or basilar artery, a collateral influx of blood may reach the compromised territory through the circle of Willis—from the opposite carotid artery via the anterior communicating artery and anterior cerebral stem and from the basilar system (or reverse) via the posterior cerebral stem and the posterior communicating artery. Thus the size of the constituent vessels of the circle of Willis can play an important part in determining the effect of carotid, vertebral, and basilar occlusion. Occlusion of one internal carotid artery in the neck is not infrequently asymptomatic, and an incidental finding at autopsy. If one vertebral artery is blocked (and this is a relatively common occurrence) little serious damage occurs if its mate of the opposite side is of good size. More than one large artery may be occluded without causing harm, e.g., one carotid and one vertebral and even, in extreme cases, both carotids.

There is also great variability in the size of the infarct resulting from post-Willis occlusion of the middle, anterior, and posterior cerebral arteries. Occasionally one or more of these vessels is entirely obstructed without clinical signs or pathologic evidence of brain infarction. At other times the infarct is so extensive as to comprise most of the anatomic territory of supply of the involved vessel; between these two extremes there may be every gradation of damage. These variations depend for the most part on the availability and size of the subarachnoid interarterial anastomoses which connect the superficial terminal branches of the middle cerebral artery with those of the anterior and posterior cerebral arteries. Large amounts of blood can be carried by these channels, sufficient at times to compensate for total occlusion of the middle cerebral artery. Thus thrombosis of the middle cerebral artery may evoke few or no signs, it may produce a devastating hemiplegia with profound sensory loss or give rise to every degree of hemiparesis or monoparesis between these two extremes. The penetrating arteries have poor anastomotic connections (virtual terminal arteries) and thus thrombosis nearly always gives rise to infarction (lacune). The size of the infarct resulting from vascular occlusion is also determined partly by factors other than anastomatic flow such as speed of occlusion (insufficient time for establishment of anastomotic flow), maintenance of systemic blood pressure, variation in the intracranial blood flow with changes in posture, etc., but these seem to be of lesser importance.

The development of clinical symptoms need not correspond directly in time to the pathologic events within an artery, as is usually assumed. Not infrequently recent cerebral infarction is found when the vascular occlusion in the carotid or middle cerebral is quite ancient indicating that factors other than a change within the vessel of supply may determine infarction or ischemia. In some cases of transient ischemia, attacks are occurring when occlusion of the lumen of the responsible vessel is already complete. This surely means that variation in the anastomotic blood flow must account for these symptoms. This lack of parallelism between the changes within the vascular lumen and the development of symptoms coupled with the great variability in the ischemic effect of vascular occlusion are the two main reasons why it is difficult to visualize at

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the bedside the anatomic substratum of the patient's clinical picture. These are important considerations for the vascular surgeon to keep in mind when, for example, he is planning surgical reconstruction of the cervical portion of the carotid artery shortly after the onset of a stroke.

*Carotid* occlusion commonly occurs first within the carotid sinus in the neck and secondary clotting or thrombosis then extends upward along the stagnant column of blood to the region of the anterior clinoid process and the cavernous sinus. When this has occurred, restitution of the channel surgically is, of course, impossible unless the clot is very recent. Thrombosis of the stem of the *middle cerebral* artery is relatively infrequent pathologically compared with internal carotid and basilar occlusion. Symptoms are produced in two ways, for the thrombus not only obstructs the flow to the superficial part of the middle cerebral territory but obstructs the mouths of the penetrating vessels running to the internal capsule and basal ganglia with the production of a "capsular hemiplegia." This latter diagnosis, a favorite often heard at the bedside, is rarely substantiated at post-mortem examination, the infarction more commonly involving the cortical and subcortical tissues. The inferior part of the posterior limb of the internal capsule (where the motor fibers lie) is supplied by the anterior choroidal artery, and even surgical ligation of the artery rarely produces hemiplegia. The upper part of the internal capsule is supplied usually by *several* penetrating branches arising from the middle cerebral stem, and occlusion of more than one of these would be necessary to produce a significant hemiplegia; however, a thrombus lying in the middle cerebral artery can do this by blocking the mouths of the adjacent branches, and actually this is the principal mechanism by which a "capsular hemiplegia" is produced. The other way in which this occurs is that sometimes an especially large penetrating artery supplies a block of capsular tissue sufficiently large that occlusion of the artery anywhere along its course results in a persistent hemiplegia. In accordance with the rule for the deposition of atherosclerosis in penetrating vessels, hypertension will nearly always be present in such a case. It should be emphasized that thrombosis of the middle cerebral artery and capsular hemiplegia are the two diagnoses most frequently made at the bedside and proved wrong at autopsy. Thrombosis of a main branch of the middle cerebral artery over the surface of the hemisphere occurs in hypertension, the occlusion usually lying near the origin of the superior or inferior divisions of the middle cerebral artery. Often the resultant infarct is small because of the influx of collateral flow via the subarachnoid interarterial anastomoses.

Thrombosis of the *posterior cerebral* artery is by no means rare and usually occurs where the artery winds posteriorly round the cerebral peduncle. In the process, penetrating branches running to the thalamus may be blocked at their mouths, and this is one of the mechanisms by which a thalamic sensory loss is produced with or without the occurrence of "thalamic pain."

Occlusion of the *basilar* artery is poorly tolerated because the clot blocks not only the flow of blood to the upper brain stem and the posterior cerebral arteries but also the mouths of the penetrating vessel entering the pons, a territory not readily reached by anastomotic flow as already noted. The clot gradu-

ally extends upward blocking branch after branch and producing deep coma and death. If the posterior cerebral stems or the posterior communicating arteries are small, obstruction of the lower part of the basilar artery may immediately result in widespread infarction.

In cases where one *vertebral* artery is vestigial, thrombosis of the remaining larger one is tantamount to occlusion low in the basilar artery. "Hidden" occlusion of the cervical portion of the vertebral artery must be a rare event since, in 150 cases personally studied at autopsy, only 1 case of obstruction was found, unilateral, and lying at the origin of the vessel from the subclavian artery. Occlusion of one or other *cerebellar* artery is more frequent than commonly supposed, particularly the anterior inferior cerebellar artery, but since no vital structures are involved and the main basilar channel remains patent, such occlusions are not dangerous to life. I find it useful in interpreting events within the vertebral-basilar system to focus on the region where the two vertebral arteries join to form the basilar artery. Atherosclerosis is particularly heavily deposited here not only obstructing one or other or both vertebral arteries or the lower basilar but also obstructing the small arterial branches running to the pontomedullary juncture, the principal theater for basilar symptomatology.

Possibly, more space has been devoted here to thrombosis than is warranted, but a thorough appreciation of the process is essential to an intelligent selection of patients for anticoagulant therapy when an attempt is being made to prevent full infarction in cerebral thrombosis.

*Cerebral Embolism.*—Cerebral embolism may be classified by cardiac origin: (a) atrial fibrillation and other arrythmias, (b) myocardial infarction with mural thrombus, (c) acute and subacute bacterial endocarditis, (d) heart disease without arrythmia or mural thrombus, (e) complications of cardiac surgery, (f) nonbacterial thrombotic (marantic) endocardial vegetations, and (g) paradoxic embolism with congenital heart disease, and by noncardiac origin: (a) mural thrombus or atheromatous material from sites of atherosclerosis in aorta and carotid arteries, (b) from sites of cerebral artery thrombosis, (c) thrombus in pulmonary vein, (d) fat, (e) tumor, (f) air, (g) complications of neck and thoracic surgery, and (h) undetermined cause.

Embolic material arising in the heart accounts for the overwhelming majority of cases. The piece of clot or thrombus breaks away to lodge in a cerebral artery at a bifurcation or narrowing. Small fragments of material which would be of no consequence if filtered out in other organs cause disaster in the brain. Emboli may enter any cerebral vessel, large or small, but in my experience they rarely enter penetrating branches, for some reason bypassing these vessels to enter the main and more superficial channels. This predilection to cortical involvement explains in part the relatively high incidence of poststroke seizures in cerebral embolism. The size of the infarct is variable, depending on the ischemia-modifying factors mentioned under thrombosis. At autopsy not infrequently no embolic material is found at the expected site although all other evidence points to the occurrence of embolism, for example the clinical story is compatible with embolism, a ready source for an embolus is found (usually the heart), infarcts are present in spleen and kidney, multiple cortical infarcts are

present in the brain, atherosclerosis and other cerebral arterial diseases are absent, and the infarct in question lies in a territory corresponding to two vessels arising at a bifurcation. At times, embolic material instead of lying at the expected site is found further distally in one or more small branches within the infarct. Thus we have been led to the conclusion that embolic material is prone to migrate or fragment or undergo complete lysis. Cases in which no embolus is found, and which we would now class as virtually certain instances of embolism, were formerly ascribed to "vasospasm" because of the absence of any obvious vascular occlusion.

Cerebral infarction can be pale (nonhemorrhagic), red (hemorrhagic), or mixed. An analysis of our pathologic data showed that hemorrhagic infarction is singularly linked to cerebral embolism. The mechanism by which this occurs is still not clear, but the great regularity with which an embolus is missing from the vessel running to a red infarct and the equally high incidence with which an embolic mass is found occluding the vessel of supply running to a pale infarct suggests that the pathogenesis of hemorrhagic infarction lies in the migration of embolic material; temporarily arrested embolus causes infarction and then drifts distally allowing influx of blood into the recently infarcted territory, and distention of capillaries and venules then occurs with leakage of red blood cells into the surrounding tissues. While this hypothesis is consonant with most of the facts, exceptional cases have been encountered, and further study of this subject is warranted. The possibility that an embolic infarct is hemorrhagic has occasioned caution in the use of anticoagulant drugs in the immediate post-stroke period. At the Massachusetts General Hospital we have had occasion to study the hemorrhagic infarct in 6 patients to whom heparin and/or dicumarol had been administered shortly after cerebral embolism had occurred, and in none of these was the degree of hemorrhage into the infarct any greater than that commonly seen in patients with hemorrhagic infarction not treated with anticoagulants. While in the majority of patients with hemorrhagic infarction, the cerebrospinal fluid is *not* blood-tinged, in a few the hemorrhage reaches greater proportions, and instead of petechial spots, small ball hemorrhages occur, and blood reaches the subarachnoid space; in cases of this kind anticoagulants are contraindicated.

Septic embolism in acute and subacute bacterial endocarditis may give rise to ordinary embolic infarcts or to miliary septic infarcts (miniature abscesses with a small admixture of blood) or mycotic aneurysms. Embolism from marantic endocarditis is a most difficult diagnosis to make. The resulting infarct is bland rather than septic. Occasionally atheromatous material is excavated from a plaque by the current of blood, and in the embolic material cholesterol clefts can be seen microscopically. Paradoxic embolism can occur only in developmental cardiac abnormalities with septal defects, and while most cases occur in childhood, a rare example is encountered at a relatively advanced age. Pathologic evidence indicates that when thrombotic occlusion of a vessel is occurring, depositing clot may break away to form a local embolus. However, this is not to be regarded as a cause of recurrent transient ischemic attacks. It would seem that cancer emboli sufficiently large to block a cerebral artery and

produce a stroke are extremely rare, and usually the source is a tumorous growth within the cardiac chambers (myxoma, carcinoma).

*Intracranial Hemorrhage.*—This may be subdivided as follows: (1) hypertensive intracerebral hemorrhage, (2) ruptured saccular aneurysm, (3) ruptured angioma, (4) trauma (extradural, subdural, subarachnoid, intracerebral), (5) hemorrhagic disorders (leukemia, aplastic anemia, thrombopenic purpura, liver disease, complications of anticoagulant therapy, hyperfibrinolysis, etc.), (6) hemorrhage of undetermined cause (normal blood pressure and no angioma), (7) hemorrhage into primary and secondary brain tumors, (8) septic embolism, mycotic aneurysm, (9) with hemorrhagic infarction, arterial or venous, (10) secondary brain stem hemorrhage (temporal lobe herniation), (11) hypertensive encephalopathy, (12) secondary to arteritis, and (13) miscellaneous rare types.

The two most frequent types of intracranial hemorrhage are, of course, hypertensive intracerebral hemorrhage and ruptured saccular aneurysm.

*Hypertensive intracerebral hemorrhage:* This results from the rupture of a small penetrating intracerebral artery. The nature of the "tear" in the artery remains unknown. Charcot and Bouchard originally described miliary aneurysms as the underlying abnormality, but these were later shown to be either mural dissections or adventitial collections of blood and not real aneurysms. Cerebral hemorrhage is often loosely attributed to rupture of an arteriosclerotic vessel without defining the meaning of arteriosclerosis. Atherosclerosis has not been shown to be related to hemorrhage, but on the other hand "hyalinosis" (a hyalin change in the media of arteries in hypertension) closely parallels the occurrence of hemorrhage. The actual site of bleeding has not often been demonstrated. In personal studies, several brain specimens in which a hemorrhage had occurred were injected with a neoprene solution shortly after death. The plastic solution pooled alongside the intracerebral hemorrhage, and upon dissection a thread of material could be traced from the pool back into the vascular lumen through a rent in the adjacent artery. Careful histologic sections of the region of rupture failed, however, to demonstrate any unusual abnormality of the vessel wall.

The escaping blood forms an oval or rounded mass within the brain displacing and compressing adjacent nerve tissue rather than destroying it completely as happens in infarction; a certain amount of dissection along tissue planes also occurs. If the patient survives, the gradual removal of the blood clot results in a significant and even excellent restitution of function since tissues were displaced and not utterly damaged. Blood which has escaped within the brain is removed very, very slowly over a period of weeks and months, and any neurologic deficit does not reverse itself quickly. Once hypertensive intracerebral bleeding has ceased, it is most unusual for bleeding to recommence, in striking contrast to hemorrhage from a ruptured saccular aneurysm which is characteristically recurrent. This difference in behavior remains unexplained. Hemorrhage seems to be an all-or-none event and rarely does any warning herald the bursting of the affected vessel. The most common sites of hemorrhage are in the putamen, thalamus, pons, cerebellum, and white matter of the cerebrum in approximately that order of frequency. Hemorrhages may be classed according to size as massive, small, "slit," and petechial. "Massive" refers to the large

hemorrhage which usually proves fatal within a day or two. A "small" hemorrhage is simply an abortive massive one and frequently is survived. "Slit" refers to the type in which a collection of blood lies just beneath the cortex along the line of juncture between gray and white matter. Petechial hemorrhages are uncommon and usually are encountered only in acute hypertensive encephalopathy and cerebral anoxia. The size of the hemorrhage probably reflects the size of the bleeding vessel although other factors are possibly of importance, for in some cases a severe neurologic deficit has come on abruptly, as if rapid bleeding had occurred, but no worsening has followed (i.e., the bleeding point for some reason quickly and effectively closed immediately as most often happen in ruptured saccular aneurysm). In an occasional case a small vessel may continue to bleed for as long as 2 weeks.

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In most hemorrhages, the cerebrospinal fluid contains blood which has reached it not by breaking into the subarachnoid space as is commonly imagined but by spilling into the ventricular system and thence into the subarachnoid space. Most often the intracranial pressure is greatly raised. Midline structures are displaced to the opposite side, the brain stem is compressed by temporal lobe herniation or distorted directly, and survival is impossible. It would seem to be a simple matter to operate as an emergency and remove the blood clot, but so far satisfactory results have not attended neurosurgical procedures.

*Ruptured saccular aneurysm:* Saccular aneurysms are thin-walled blisters lying for the most part at branchings and bifurcations of the circle of Willis. Ninety per cent of aneurysms lie on the anterior part of the circle at the anterior communicating artery, at the junction of the posterior communicating artery and the internal carotid artery, at the first bifurcation of the middle cerebral artery, or at the bifurcation of the internal carotid artery. Their average size is 8 to 10 millimeters with a range from 2 or 3 millimeters up to 3 cm. In 15 per cent of cases there is more than one aneurysm, the multiple aneurysms all lying on one side of the circle or being distributed on both sides.

Their walls consist only of epithelium and adventitia, the muscle and elastic layers being entirely wanting. They are rarely found in children but increase with age to reach a peak incidence in the age groups 35 to 55. Thus they are not formed congenitally but gradually evolve on the basis of a developmental defect in the media at bifurcations of arteries. Why cerebral arteries should be prone to their formation and not vessels elsewhere in the body remains a puzzle. There is a slight but definite correlation between aneurysmal formation and the presence of polycystic kidneys. Hypertension is present more often in aneurysm cases than in the average population, but not infrequently the blood pressure is not elevated in the slightest.

Rupture must be due to a sudden giving-way of either the endothelium or the overlying collagenous connective tissue. In most cases, the hemorrhage must cease as promptly as it began; otherwise survival would be precluded as blood continued to flood into the subarachnoid space. The quick return of consciousness in many cases (a few minutes or so) also attests to this idea. However, recurrence of bleeding in the next days, weeks, months, or years is the rule; the reason nature fails to maintain the temporary arrest of bleeding is an

enigma. The blood may not only enter the subarachnoid space but also dissect into the adjacent brain tissue (meningo-cerebral hemorrhage) or even into the ventricular system (meningo-cerebral-ventricular hemorrhage). The problem in therapy is to deal effectively with the aneurysm before rebleeding occurs, but unfortunately early operation carries with it a high risk. In many cases of ruptured aneurysm, focal neurologic signs appear which are caused not by hemorrhage into brain tissue but by ischemia or infarction in the territory supplied by the vessels on which the aneurysms lie. The mechanism of this is not understood, but fortunately in many instances the deficit is completely reversed.

This foregoing review of the pathophysiology of cerebrovascular diseases, although admittedly incomplete because of the limitations of space, encompasses chiefly the viewpoint of the neuropathologist concerned with discerning in the pathologic anatomy of his specimens clues to a better understanding of the pathogenesis, diagnosis, and treatment of these diseases.

## DIAGNOSIS

The clinical hallmark of cerebrovascular disease is "the stroke," a term which connotes the sudden development of a focal neurologic deficit. Depending on the cause (thrombosis, embolism, hemorrhage) the speed of evolution varies from a few seconds to minutes, hours, or, at the most, a few days. In some cases, the neurologic signs vanish dramatically as quickly as they came; more often, if the patient survives, stabilization first occurs followed by some degree of recovery. This *temporal profile of a stroke*—sudden development, stabilization, and recovery (sometimes dramatic improvement)—is highly characteristic and stamps the process as vascular. Strokes which come on over a period of several days usually progress in a stepwise or fluctuating fashion (a series of typical temporal-profiles-in-miniature) rather than smoothly. A slow gradual downhill course over a period of days or weeks indicates that the process is probably not vascular in nature.

Very few other neurologic illnesses have a temporal profile which mimics that of cerebrovascular disorders. Tumor, infection, inflammation, degeneration, and nutritional disorders are not likely to manifest themselves precipitously. In trauma, of course, a sudden insult occurs, but usually injury is readily recognizable as the cause. Multiple sclerosis and other demyelinative diseases often have abrupt episodes of exacerbation but are seldom as sudden in onset as vascular diseases, and for the most part they occur in a different age group and clinical setting.

The neurologic deficit in a stroke depends, of course, on the location of the infarct or hemorrhage in the brain, and the size of the lesion. No symptoms or signs or clinical picture can be said to be diagnostic of vascular insult, but the occurrence of a severe hemiplegia is so typical that a stroke immediately suggests itself. However, a stroke, of course, gives rise to many manifestations other than a hemiplegia, e.g., numbness, loss of sensation, dysphasia, diplopia, dysarthria, dizziness, impaired vision, etc., any of which can result from other neuro-

logic diseases; therefore, features of the illness other than, or in addition to, the neurologic picture must be relied upon in interpreting the process. In practice it is usually the entire constellation of clinical features that establishes the diagnosis of vascular disease. Often the patient is elderly, and arterial hypertension is present. There may be evidence of vascular disease of the heart, lower limbs, or the aorta. Diabetes mellitus may be present, increasing the patient's liability to atherosclerosis. A source of emboli may be evident. Many strokes are preceded by transient warning episodes of weakness, numbness, dizziness, etc., and these attacks, if they are nonconvulsive, should always suggest thrombotic cerebrovascular disease. The classical lateral medullary syndrome is almost always a product of vascular insult. Last, the presence of blood in the cerebrospinal fluid signifies that the process is vascular, and diagnostic deductions can proceed from that vantage point.

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TABLE I. DEVELOPMENT OF THE CLINICAL PICTURE IN 125 CASES OF CEREBRAL THROMBOSIS

| | | | |
|---|---|---|---|
| 1. | Transient ischemic attacks progressing to a persistent neurologic deficit, major or minor | 53 | (42%) |
| 2. | Stepwise development of a stroke with or without transient ischemic attacks | 23 | (18%) |
| 3. | Transient ischemic attacks only | 17 | (13%) |
| 4. | Rather abrupt onset in a matter of hours with or without fluctuations | 14 | (11%) |
| 5. | Development of a limited stroke followed by transient ischemic attacks | 11 | (9%) |
| 6. | Slow, gradual evolution over several days with minor or no fluctations | 7 | (5%) |

From these general remarks we now proceed to a brief discussion of the diagnostic features of cerebral thrombosis, cerebral embolism, and cerebral hemorrhage. In each case the neurologic picture will be first described followed by some of the more characteristic features of the stroke.

*Cerebral Thrombosis.*—A vast array of symptoms and signs occurs in cerebral thrombosis depending on the territory involved and the extent and severity of the ischemia. The territory of any vessel may be affected, large or small, deep or superficial. In the carotid system, unilateral signs predominate: hemiplegia, hemihypesthesia, hemianopia, aphasia, agnosia, and apraxia. In the basilar system, hemiplegia may also be found, but more commonly, there are bilateral signs motor and/or sensory in combination with a disturbance of cranial nerves, cerebellum, or other structures localized in or related to the brain stem. In identifying vascular syndromes, it is important to determine if the signs and symptoms indicate unilateral or bilateral lesions.

*Middle cerebral artery:* Chief neurologic features are contralateral hemiplegia, hemianesthesia, homonymous hemianopia, and paralysis of conjugate lateral gaze to the opposite side; if the dominant hemisphere is affected, there will be aphasia and ideational apraxia; if the nondominant hemisphere is involved, there will be apractognosia of the minor hemisphere (anosognosia, imperception of the left side of the body and the environment, constructional apraxia, loss of topographic sense, etc.), and motor impersistence.

*Middle cerebral penetrating branches:* Chief neurologic features are hemiparesis or hemiplegia without hemianopia and probably without sensory change (usually a lacune is formed in the upper internal capsule or corona radiata).

*Anterior cerebral artery:* Chief neurologic features are paralysis and sensory loss of the opposite lower limb, lesser involvement of the contralateral upper limb, mental changes such as forgetfulness, some degree of akinetic mutism, motor apraxia, sucking and grasping reflexes, gegenhalten, and incontinence of bowel and bladder.

*Internal carotid artery:* In the majority of cases the neurologic signs are those of the middle cerebral artery, but if the anterior communicating artery is unusually small, the picture of anterior cerebral infarction is added, producing a moderately stuporous condition in the patient. The carotid artery supplies the optic nerve and retina, and there may occur the picture of occlusion of the central retinal artery, transient monocular blindness, and reduced pressure in the central retinal artery. Pulsation may be lacking in the common, internal, or external carotid arteries, and a bruit may be heard in the opposite patent carotid artery if the stethoscope is placed over the eye. Palpation of the internal carotid artery can also be carried out in the pharynx.

*Posterior cerebral artery:* Contralateral homonymous hemianopia with or without scintillations is the main result of infarction of the calcarine cortex. When the dominant hemisphere is involved there may be alexia, impairment of revisualization, color blindness, disorientation, poor memory, and visual agnosia. Bilateral lesions may cause total blindness without the patient being aware of it, and he may vividly describe what he "sees" before him.

When more centrally lying structures are involved, one may find a transient hemiplegia, thalamic sensory loss, thalamic pain, hemiballismus, choreoathetosis, cramplike spasms of the hand, cerebellar signs, third-nerve palsy, paralysis of vertical gaze, and occasionally peduncular hallucinosis (brightly colored scenes and people).

*Vertebral artery:* Occlusion of this vessel usually produces few symptoms but may give rise to (1) the lateral medullary syndrome (pain and numbness of the side of the face, dizziness, nausea, vomiting, dysphagia, hoarseness, cerebellar ataxia on ipsilateral side, Horner's syndrome (ipsilateral), loss of pain and temperature on opposite side of body, or (2) hemiplegia due to involvement of the pyramid of the medulla, or (3) the medial medullary syndrome (paralysis and atrophy of one-half of the tongue, paralysis of the contralateral arm and leg, and sensory loss on the opposite half of the body.

Bilateral vertebral artery occlusion is equivalent to basilar artery occlusion.

*Basilar artery:* This artery via its pontine and cerebellar branches supplies the motor fibers descending from the cerebral cortex, the sensory fibers carrying the impulses for pain, temperature, and deep and superficial touch from the periphery upward to the thalamus, the cerebellum, and the nuclei and tracts of the third, fourth, fifth, sixth, seventh, and eighth cranial nerves. In the complete basilar syndrome there is paralysis of all four extremities as well as of the muscles of swallowing and speaking, and usually deep coma ensues. If consciousness is retained, it may be possible to demonstrate cerebellar ataxia, diplopia, nystagmus, and sensory loss on one or both sides of the body.

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*Superior cerebellar artery:* Chief neurologic signs are severe ipsilateral cerebellar ataxia, nausea and vomiting, Horner's syndrome, and loss of pain and temperature over the opposite side of the body.

*Anterior inferior cerebellar artery:* Neurologic signs include ipsilateral cerebellar ataxia, Horner's syndrome, spinning dizziness, ipsilateral deafness, facial palsy, and sensory loss over the face. Nausea, vomiting, tinnitus, and nystagmus may be associated.

*Posterior inferior cerebellar artery:* Ipsilateral cerebellar ataxia and in some cases the lateral medullary syndrome (see vertebral artery) are chief neurologic signs.

*Basilar pontine branches:* Hemiplegia (or hemiparesis) and possibly mild sensory loss (usually a lacune is formed in the basis pontis) are neurologic signs.

It should be repeated here that because of the various ischemia-modifying factors previously referred to and depending on the site along the vessel at which the occlusion lies, there is great variability in the number and severity of the listed manifestations which occur as a result of thrombosis of any stated vessel, and indeed partial syndromes are the rule.

*Criteria for the diagnosis of cerebral thrombosis:*

1. Occurrence of prodromal "warnings" in the form of attacks of transient cerebral ischemia. Since these episodes of paralysis, numbness, dizziness, etc., never precede an oncoming cerebral hemorrhage and are uncommon in embolism, they are the single most reliable indicator of thrombosis with atherosclerosis (transient ischemic attacks will be discussed in more detail later).

2. A stepwise, saltatory or fluctuating evolution of the clinical picture occurs in 90 per cent of cases of cerebral thrombosis (Table I). For example, a total hemiplegia develops intermittently, not abruptly or gradually; weakness of the hand may appear first, and after improving for hours or days, a further increment of paralysis is added which in its time may remit only to have total paralysis supervene shortly. This type of hesitating "stuttering" progression is not seen in intracranial hemorrhage or in embolism.

3. The occurrence of a rapid reversal of the neurologic deficit. Ischemia resulting in mild easily reversible damage can recover in hours or days if the circulation is restored. While this can happen just as frequently in cerebral embolism, it is not seen in hemorrhage, since blood which has leaked into the tissues cannot be removed quickly.

4. Clear cerebrospinal fluid. Thrombotic infarction virtually never results in a bloody fluid, the only possible way in which this could occur being via the production of a severe hemorrhagic infarct.

5. Relative preservation of consciousness. The preservation of mental alertness in the presence of a severe hemiplegia suggests ischemic infarction rather than hemorrhage; however, in some cases of intracerebral hemorrhage, the patient is paralyzed, and there is blood in the spinal fluid when the patient is sufficiently alert to converse and cooperate in the examination. On the other hand, basilar artery thrombosis can result in deep coma, so the rule clearly has its limitations.

6. Onset of symptoms during hypotension (postural, blood loss, etc.)

7. The occurrence of additional insult to approximately the same vascular territory previously affected by a partial stroke; that is, a new neurologic deficit appears to arise adjacent to an old one, as is frequently seen in vertebral-basilar disease, where some patients may show additional increments of neurologic disturbance for up to 7 or 8 years.

8. White-walled retinal arteries. Occasionally, the proximal segments of the branches of the retinal artery are densely white, and the blood column is narrowed. This, at present, appears to be correlated with severe cerebral atherosclerosis and the presence of lacunar disease.

9. Certain constellations of symptoms and signs are rarely seen in embolism or hemorrhage and are therefore almost pathognomonic of cerebral thrombosis, for example the lateral medullary syndrome. Monoplegia, pure motor paralysis, isolated motor aphasia (anarthria), isolated sensory aphasia, and isolated hemianopia are rarely due to hemorrhage and usually indicate infarction.

10. The patient is elderly or has signs of atherosclerosis elsewhere, especially in the coronary or peripheral vessels.

11. The presence of disorders commonly associated with atherosclerosis—hypertension, diabetes mellitus, xanthomatosis, hypercholesterolemia.

*Cerebral Embolism.*—In cerebral embolism the neurologic picture is similar to that described for each of the cerebral arteries under cerebral thrombosis, with the exception that emboli do not often enter penetrating vessels.

*Criteria for diagnosis of cerebral embolism:*

1. Cerebrovascular symptoms develop suddenly (within seconds or a few minutes). Embolic plugs seem to reach their occluding position with a minimum delay for adjustment and the patient moving his limbs normally one moment is rendered hemiplegic the next.

2. The absence of prodromal manifestations in most cases. Unlike cerebral thrombosis, cerebral embolism is not preceded by "warnings" in the preceding days or weeks, and in most instances no transient fluctuations take place at all. However, we are beginning to recognize that unilateral headache may precede the development of an embolic stroke by as long as 24 to 36 hours and also that one or several transient ischemic attacks may occur within a few hours of the onset of the paralysis but not longer than 12 hours before. The explanation for some of these prodromal episodes is occlusion of the internal carotid artery in the neck, collateral influx via the circle of Willis permitting a temporary restitution of function.

3. Rapid improvement from single stroke. As noted under thrombosis, the deficit resulting from hemorrhage resolves slowly, whereas ischemia can be relieved in a matter of minutes, hours, or a few days. Embolic material may become temporarily arrested at a bifurcation resulting for example in a hemiplegia, but in a matter of minutes, fragmentation or migration takes place, the particle drifts into a peripheral twig, circulation is restored to most of the territory, and the neurologic deficit clears dramatically. Hence, cerebral embolism is one of the causes of a single transient ischemic attack. However, if two or more identical brief episodes occur in the same territory on successive days or at a longer interval, embolism is unlikely.

4. A source of emboli is evident, usually in the heart (either cardiac arrythmia or infarction).

5. Evidence of recent embolism in other organs (spleen, kidney, extremities, intestine, or lung) or in several regions of the brain in different cerebrovascular territories. While embolism to an extremity is usually easily recognized, this is not necessarily so for lung, spleen, kidney, or intestine, and one must be on the alert and methodically inquire about relatively minor insults which have been dismissed as a "cold," "grippe," pyelonephritis, pyelitis, or indigestion. At post mortem in embolism cases infarcts which apparently caused no important symptoms are extremely common in one or more of the above organs.

6. The occurrence of a stroke with sudden onset in a young person ostensibly free from atherosclerosis and without syphilis and arteritis.

7. Clear cerebrospinal fluid. Infarcts resulting from cerebral embolism like those in cerebral thrombosis usually do not cause bloodying of the spinal fluid, and the only exception is the excessively hemorrhagic infarct which is rather rare. Ordinary hemorrhagic infarcts do not cause blood in the spinal fluid although those situated on the undersurface of the cerebellum are occasionally associated with xanthochromia.

8. Relative preservation of consciousness compared with hemorrhage. As in cerebral thrombosis an extensive neurologic deficit may be present when the patient is relatively alert, whereas in hemorrhage, stupor or coma would exist in most cases. However, when embolism to the upper bifurcation of the basilar artery occurs, the patient may be plunged abruptly into deep coma due to infarction of the upper brain stem.

*Hypertensive Intracerebral Hemorrhage.*—Because hemorrhages occur in deep structures (putamen, thalamus, pons, cerebellum, etc.) and cause their mischief partly through pressure on adjacent tracts and nuclei, they cannot be expected to evoke a clinical picture which can be interpreted readily or exactly in terms of the vascular territories described in thrombosis. Their size also is, of course, of great importance in determining the neurologic deficit. Nonetheless, the neurologic manifestations approximate those which would result from a relatively similarly situated infarct. Usually, a large hemorrhage in one hemisphere quickly produces a hemiplegia and deepening coma, whereas a small hemorrhage might occasion only a hemiparesis and hemianesthesia, and in addition aphasia if the lesion were on the dominant side. A large hemorrhage in the pons or cerebellum rapidly produces deep coma and death. However, in each of these sites, a smaller hemorrhage can be survived. Small hemorrhages in the posterior inferior region of the thalamus are not rare, and the prognosis is good, although the hemorrhage opens into the ventricular system.

*Criteria for diagnosis of hypertensive intracerebral hemorrhage:*

1. Hypertension is present by definition. Usually the pressure remains elevated until relatively late in the course of the stroke. While the level of pressure is usually very high, it may be only modestly elevated.

2. Bloody cerebrospinal fluid. The finding of gross blood in the cerebrospinal fluid with xanthochromia in the supernatant fluid greatly simplifies the differential diagnosis of strokes. When the fluid is clear, one must constantly

consider the possibility that a hemorrhage has occurred which has not reached the cerebrospinal fluid (this is true not only of a hypertensive hemorrhage, but also one caused by angioma, tumor, hemorrhagic infarct, etc.). On the other hand, when blood is present, the possibility of a traumatic puncture must be entertained, and especially is this the case when only a small number of red cells is present (40 to 300) and xanthochromia is faint. A comparison of carefully performed counts of the red cells in the first and third tubes to determine if the admixture of blood is even is the only reliable way to identify a traumatic tap, a most important matter when the administration of anticoagulants is anticipated. In subarachnoid hemorrhage, the cerebrospinal fluid is usually under increased pressure and is said not to clot because defibrination has taken place in the subarachnoid space. In a bloody tap, the pressure is usually low or normal, and the fluid may clot.

3. Rapid but gradual evolution of hemiplegia or other neurologic deficit over a period of minutes or hours, occasionally days. In most instances, a careful history will indicate that the clinical picture has come on gradually over a perceptible period, usually 1 to 2 hours as the extravasation of blood continued. The patient may first feel something awry within the head, then in progression the hand becomes clumsy, and in the worst cases consciousness is lost. This relentless steadily downhill course is extremely rare in thrombosis. In embolism, the full deficit appears immediately, and if coma is to follow because of brain swelling and tentorial herniation it comes on in the next 2 or 3 days, and a clear appreciation of the early course will help to distinguish the process from hemorrhage.

4. Rapid progression to coma. Hemorrhage much more commonly than embolism and thrombosis leads to coma in the presence of an extensive neurologic deficit, but exceptions occur.

5. Onset during activity or waking hours. It is rare for hypertensive hemorrhage to have its onset during sleep or rest possibly because the blood pressure is slightly lower under such circumstances. A personal analysis of 54 cases of cerebral hemorrhage showed that in only one had the patient awakened with a stroke.

6. Severe headache has long been held to be a symptom of intracerebral hemorrhage, but I have not been able to satisfy myself that it is a useful indicator since thrombosis and embolism both occasion headache (sometimes of major proportions, but usually not) whereas headache is virtually absent in many cases of hemorrhage, although the spinal fluid is grossly bloody. There is need for a more exact study of this subject.

7. Stiffness of the neck on forward flexion is present in a high percentage of hemorrhage cases when carefully tested for and nearly always absent in thrombosis and embolism.

8. The presence of preretinal (subhyaloid) hemorrhages. Although these are more common in cases of ruptured saccular aneurysm, they may occur in hypertensive intracerebral hemorrhage, and if present they are at least diagnostic of a violent intracranial hemorrhage.

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*Ruptured Saccular Aneurysm.*—The most characteristic picture of ruptured saccular aneurysm is the presence of grossly bloody spinal fluid with little or no accompanying focal neurologic deficit, whereas in intracerebral hemorrhage the tendency is just the reverse, the neurologic deficit predominating. This general statement has high validity but overlooks the fact that unconsciousness—brief or prolonged, drowsiness, confusion, and lack of memory all of which are commonly present represent focal damage to the hypothalamus resulting from high intracranial pressure locally. If lateralizing is substituted for focal, the rule again needs qualification, for blood spurting from the aneurysm may burrow into the brain tissue producing lateralizing neurologic signs and persistent stupor. Also, not infrequently, ischemic infarction occurs in the territory of the artery on which the ruptured aneurysm lies producing a neurologic deficit usually without persistent stupor and coma. Furthermore, careful inquiry shows that a high percentage of aneurysm cases have a relatively minor and/or evanescent focal neurologic deficit immediately after the hemorrhage occurs. When a neurologic deficit occurs it depends for the most part on the site of the aneurysm. Blood rupturing into the frontal or temporal lobes produces a hemiplegia usually associated with deep stupor. If the hemorrhage is so extensive as to break directly through into the ventricular system, coma and death follow. Hemorrhage between the hemispheres from an anterior cerebral aneurysm is likely to cause "akinetic mutism" or a closely similar state. Ischemic infarction in the middle cerebral territory may produce hemiplegia or monoplegia, anarthria or dysarthria, or aphasia; a transient hemiparesis or aphasia may be noted at the onset of the illness. One or both anterior cerebral arteries may become occluded, leading to paralysis of the legs, incontinence, bifrontal torpor (motor and mental inertia), profound dementia, and grasping and sucking reflexes. Occasionally at the time of rupture of an aneurysm of the anterior communicating artery, transient weakness of one or both lower extremities will be observed. Palsy of the third nerve is diagnostic of an aneurysm arising at the origin of the posterior communicating artery from the internal carotid artery.

*Criteria for diagnosis of ruptured saccular aneurysm:*

1. Grossly bloody spinal fluid. Rupture of an aneurysm never occurs without some blood leaking into the subarachnoid space. The fluid contains more red blood cells as a rule than in intracerebral hemorrhage.

2. Sudden onset of severe headache. If consciousness is not lost at the onset, the patient will, in 9 of 10 cases, complain of an agonizing headache. If the patient has lost consciousness for a short or long time he will complain of headache when alert enough to be aware of it.

3. A relatively transitory disturbance of consciousness. Although coma and stupor may be prolonged, in many cases the period of collapse and unconsciousness is brief—a few minutes or so—after which the patient "comes to" and complains of headache. This clinical story is virtually diagnostic of ruptured aneurysm. At the onset, the patient may fall and suffer a complicating head injury, and it may be difficult to decide on the nature of the illness if this brief collapse in ruptured aneurysm is not kept in mind.

4. A relative absence of lateralizing neurologic signs. This has been discussed above.

5. Stiffness of the neck on forward bending.

6. Onset during the waking state in 95 per cent of cases.

7. Preretinal (subhyaloid) hemorrhages. These smooth-edged dense "blobs" of blood overlying the retina indicate intracranial hemorrhage, and if the patient is conscious, the diagnosis of ruptured aneurysm is almost a certainty (occasionally a ruptured hemangioma will also cause this).

8. Intracranial hemorrhage in patient with normal blood pressure.

9. Absence of prodromal focal neurologic signs. Except for pressure on adjacent structures, e.g., the third nerve, optic chiasm or optic nerves, or the occurrence of minor hemorrhages preceding the main rupture, there is no warning that a major hemorrhage will occur.

10. The association of polycystic kidneys or coarctation of the aorta with intracranial hemorrhage points to the possible presence of a saccular aneurysm.

11. A history of one or more similar episodes of hemorrhage previously. Hypertensive intracerebral hemorrhage is devastating so frequently that to have a patient survive two hemorrhages would be extremely rare.

*Ruptured Angioma.*—An angioma consists of a tangle of abnormal vessels which form an abnormal communication between arteries and veins. Its presence is announced in most instances between the ages of 10 and 30 years by either the onset of epilepsy or the occurrence of hemorrhage. In the latter event, bleeding usually takes place both into the subarachnoid space and into nervous tissue, producing a focal neurologic deficit whose nature, of course, depends on where along the neuraxis the malformation lies—cerebrum, thalamus, vein of Galen, midbrain, pons, cerebellum, medulla, or spinal cord.

*Criteria for diagnosis of bleeding from angioma:*

1. Stroke in a young patient with bloody cerebrospinal fluid in the absence of hypertension.

2. History of focal epilepsy or focal cerebral symptoms. Jacksonian seizures are not a forerunner of hypertensive intracerebral hemorrhage or rupture of a saccular aneurysm.

3. The presence of a cranial bruit, heard best by listening with the stethoscope placed over the eyeball or over the mastoid process, usually indicates a large tangle of abnormal vessels easily demonstrable by arteriography. Small angiomas 2 cm. or less in diameter may not be audible. A brief systolic bruit may occur in a small minority of saccular aneurysms after rupture but the angiomatous murmur is usually a longer, more continuous sound. The patient himself sometimes hears the bruit, but even an extremely loud murmur may be inaudible to him.

4. Preretinal (subhyaloid) hemorrhages indicate intracranial bleeding, and if the patient is normotensive, a ruptured aneurysm or angioma will be found.

5. Characteristic calcification in skull x-ray. In some angiomas that have bled in the past, a curvilinear deposition of calcification may be seen in the plain x-rays of the skull and is virtually diagnostic of angioma.

6. An angiomatous malformation of the retina accompanies a minority of intracranial angiomas.

7. A history of several subarachnoid hemorrhages, four or more, usually means that an angioma is present rather than a saccular aneurysm.

8. Rarely one of the following may be encountered: the slowly progressive development of a neurologic deficit, onset of hemorrhage during an ordinary migrainous attack, dilated arterial or venous channels around the orbit, exophthalmos, angiomas on the face or ears, etc.

*Remarks on Special Aspects of Diagnosis of Cerebrovascular Diseases.—*

*Recurrent transient ischemic attacks (formerly called cerebral vasospasm):* Reports in the current literature clearly indicate that anticoagulants are of value in cerebral thrombosis when administered at the stage of recurrent transient ischemic attacks or early in the course of the *stroke-in-evolution* (this term refers to the stepwise, "stuttering," or start-and-stop progression of a stroke in cerebral thrombosis). Because recurrent transient ischemic attacks are almost diagnostic of cerebral thrombosis, and since they may constitute the only warning before a persistent paralysis comes on, it is important to be acquainted with their main features.

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Transient ischemic attacks may precede, accompany, or follow the development of a stroke, or they may occur alone, i.e., without leading to persistent signs. They can arise in association with thrombosis of any cerebral artery, deep or superficial; common carotid, internal carotid, middle cerebral, anterior cerebral, vertebral, basilar, posterior cerebral, the cerebellar arteries, and the penetrating branches to the deep structures of the basal ganglia and brain stem. In my material they are encountered slightly more commonly in the vertebral-basilar system.

The neurologic features of the episode indicate the territory or artery involved and are fragments borrowed from the stroke which is often approaching. In the carotid system there may be unilateral weakness or numbness of the opposite face, hand, and leg or any part thereof, dysphasia, or dysarthria when the dominant hemisphere is affected, confusion, veering, monocular blindness or blurring of vision, scintillating scotomata, headache, and possibly focal epileptic seizures (doubtful).

In the vertebral-basilar system, the picture is extremely diverse, and the following may be recognized: weakness or paralysis of one or both sides of the body or part of one or both sides, numbness of all or part of one side of the body (bilateral numbness is rare except around the mouth), dizziness, diplopia (vertical or horizontal), dark vision, blurred vision, tunnel vision, partial or complete blindness, scintillating scotomata, pupillary dilatation, ptosis, paralysis of gaze, dysarthria, speechlessness, dysphagia, staggering gait, veering, headache, noise or pounding in the ear or in the head, head or face pain, peculiar sensations in the head (a band around the head, a block of cement, a wire being tightened around the head), vomiting, hiccoughing, memory lapses, confused behavior, impaired hearing, deafness, sweating, facial redness, a feeling of movement or twitching (rare), unconsciousness (rare), and phenomena suggesting the aura

of temporal lobe seizures (rare). The commonest of these are dizziness (vestibular in type), diplopia, dysarthria, numbness around the mouth, weakness of the limbs on one or both sides, and difficulty in seeing.

An ischemic attack may involve many cerebral structures and produce a host of manifestation as in some dramatic cases of basilar artery disease when total paralysis of face, arms, and legs occurs with dizziness, diplopia, and dysphagia. In other cases, the signs may be extremely limited, for example, the slightest degree of diplopia or discrete attacks of numbness involving one side of one lip or one thumb only. This may be interpreted to mean that blood flow can be compromised in many branches of a main trunk or in a small twig.

Transient ischemic attacks may last for a few seconds up to several hours, the most common duration being a few seconds up to 5 or 10 minutes; it is uncommon for recurrent attacks to last for more than 30 minutes. Sensations that come and go in a second or in a "flash" are usually not ischemic in nature, although some patients report very brief periods of numbness between their major attacks. There may be only a few attacks or several hundred. A stroke may ensue after the second one or be postponed until hundreds have occurred over a period of weeks or months. Not infrequently the attacks gradually cease, and no important paralysis occurs. Transient symptoms which appear shortly after arising in the morning (or during the night to go to the bathroom) are especially liable to be followed by a stroke. The attacks may all take approximately the same pattern, or they may vary considerably in detail although maintaining the same basic pattern. For example, weakness or numbness may involve face and fingers in some episodes and only the face in others; or dizziness and diplopia may occur in some attacks and only one of them in other attacks. In basilar artery disease each side of the body may be affected simultaneously, or a definite march or spread from one region to another can occur in a period of 10 to 60 seconds. Each attack may cease abruptly or fade gradually.

The onset of attacks in some cases is clearly related to standing up after lying or sitting. They are especially frequent shortly after arising in the morning or after eating. They have been encountered in relation to exercises, exertion, emotional outbursts of anger or joy, and during bouts of coughing. However, in many instances no precipitating factor or circumstance can be recognized, as in one patient whose paralysis came on anew every half hour for several hours, although he seemed to be maintaining the same position in bed, and no difference in the brachial blood pressure could be measured during and between attacks.

There would seem to be no doubt that these brief episodes are ischemic in nature and not primarily a seizure phenomenon. Ophthalmoscopic observations made during episodes of transient monocular blindness show arrest of the blood flow in the retinal arteries and breaking up of the venous column to form the well-known "box-car" pattern. By analogy, one might visualize a transient cessation or virtual cessation of blood flow locally during attacks involving other arterial territories. The mechanism of the attacks is far from clear. Vasospasm, a fall in the systemic blood pressure, local embolization, and failure of collateral flow distal to the site of thrombosis because of sludging, have all been invoked. Anticoagulants appear to abolish the attacks in nearly all cases.

Transient ischemic attacks must be differentiated from focal cerebral (epileptic) seizures, Menière's syndrome, paralytic migraine, Stokes-Adams attacks, carotid sinus reaction, transient global amnesia, akinetic falling spells of the aged, and cerebral embolism. On rare occasions, ischemic episodes may be confused with tussive syncope, multiple sclerosis, cataplexy with narcolepsy, the brachial distress of hiatus hernia, cervical disk disease, unusual symptoms in angina pectoris, severe postural hypotension, recurrent pulmonary embolism, hemangioma of the brain stem, and other assorted conditions.

Frank motor convulsions are extremely rare in ischemic attacks. Occasionally the muscles of the affected part tremble mildly, or there is a feeling of movement, distortion, or drawing, but no patient of mine has described gross jerking or twitching. Usually, the affected limb simply becomes weak. It must be extremely rare that temporary paralysis of a limb or of one side of the body is the sole manifestation of a cerebral seizure. Incontinence of bowel and bladder, tongue-biting, oral frothing, cyanosis and residual soreness, and sleepiness are rarely if at all encountered in ischemic attacks. "Unconsciousness" is virtually unknown, and in the great majority of cases, the patient remains alert. Distinguishing ischemic episodes from seizures on the basis of sensory phenomena is more equivocal for numbness, and visual scintillations are probably not much different in the two conditions. In making a differentiation it is well to rely on associated signs and symptoms, e.g., diplopia, transient monocular blindness, etc., suggest ischemia; pallor, tasting movements, impaired alertness, etc., suggest a seizure.

When dizziness is the only complaint, it may be impossible to decide if it is the result of transient ischemia or part of a Menière's type of illness. The differentiation is easy if, on one hand, there are associated brain-stem signs or on the other, tinnitus and deafness are present to complete the Menière's triad. Occasionally, in vascular crises the eighth nerve is rather selectively involved producing deafness, dizziness, and tinnitus, but I have not yet encountered a case in which at least a trace of some other brain-stem manifestation such as numbness of the face or diplopia was not present.

Ischemic episodes are occasionally wrongly diagnosed as migraine, particularly when attacks of visual scintillations are combined with a unilateral headache in disease of the posterior cerebral artery. It should be appreciated that headache is a frequent accompaniement of cerebral thrombosis whereas migraine having its onset for the first time in the fifties or sixties is an uncommon event. The diagnosis of migraine-aura-without-headache is also at times incorrectly invoked as the explanation for transient visual flashes or zig-zags without headache in elderly persons suffering from vascular disease.

Stokes-Adams attacks (and hypersensitivity of the carotid sinus reflex) bear only a superficial resemblance to transient ischemic attacks but must be considered when a patient is subject to collapsing spells, of which no adequate description is available. The demonstration of carotid sinus hypersensitivity does not necessarily mean that the cause of the patient's attacks has been discovered, for it must be remembered that in the elderly the sinus region is not infrequently sensitive to massage and the two disorders may co-exist. Cardiac

asystole will not often produce recurrent focal neurologic manifestations (weakness, numbness, diplopia, etc.) whereas transient ischemic attacks do not lead to unconsciousness and convulsive movements. A careful minute-by-minute description of the attack will usually allow the correct diagnosis to be reached.

*"Cerebral arteriosclerosis":* The diagnosis of cerebral arteriosclerosis is frequently made in elderly patients who are showing a gradual impairment of memory, vague personality changes, nocturnal confusion, or slowing up of their motor and mental activity, the inference being either that small strokes have occurred in strategic regions of the brain subserving the mind but sparing motor and sensory function and thus producing no focal weakness or numbness or that "arteriosclerotic" plaques by sheer numbers have so reduced the cerebral blood flow that certain parts of the brain are malfunctioning because of some degree of ischemia. This time-honored diagnostic precept when subjected to clinicopathologic scrutiny is proving to be wholly unreliable. Even the term arteriosclerosis is unsatisfactory, for it leaves some doubt whether the disease atherosclerosis is being referred to in which case it would have been preferable to so designate it rather than using the generic term arteriosclerosis, which in its broad connotations includes several different arterial diseases. Even if by arteriosclerosis one means atherosclerosis, it still is incorrect to ascribe to it the manifestations mentioned. Since atherosclerosis is, in most instances, silent until thrombosis occurs and a stroke supervenes, it will give rise to neurologic infirmity only insofar as it causes strokes, in which case a history will be obtained of a sudden insult of a vascular nature, or on examination there will be either frank signs of a former stroke or some more subtle neurologic deficit such as increased tendon reflexes in one or more limbs, a Babinski sign, a homonymous hemianopia, dysphasia, nystagmus, and so forth. In the absence of evidence of one or more strokes by history and examination, persistent nervous system manifestations like loss of memory, personality changes, etc., are not to be laid at the door of atherosclerosis. A gradual development of symptoms and a lack of remissions are contrary to vascular disease. Likewise, without the same evidence, aberrations of the aged are not to be loosely attributed to small strokes in silent areas.

Failing memory in the elderly is usually caused by Alzheimer's disease (senile plaque encephalopathy) or some related degenerative process and not by cerebral atherosclerosis. Even when the brain contains countless lacunar lesions as a result of atherosclerosis and hypertension, it is remarkable how often the patient's mind is relatively spared compared with the motor system, unless a severe dysphasia has impoverished the patient's mind. To paraphrase an old idiom "small strokes lick the mind and bite the body, Alzheimer's disease licks the body and bites the mind (memory)." It should be pointed out that dysphasic patients are often simply categorized as demented without the actual focal nature of their symptoms being recognized.

In similar vein, the easy practice of ascribing dizziness, headache, and various transient symptoms tc the vague entity "hypertensive encephalopathy" might also be criticized. An exact diagnosis is preferable: cerebral thrombosis, embolism or hemorrhage, transient ischemic attack, Menière's syndrome, etc. The designation acute hypertensive encephalopathy is retained, however, to

refer to the distinctive acute clinical syndrome characterized by severe hypertension, nausea, vomiting, headache, confusion, seizures, coma, and often death.

*Special diagnostic measures:* The routine use of arteriography has been recommended in all stroke cases. This advice may have some basis if it is part of a carefully designed scientific investigation of this group of diseases, possibly seeking to perfect or devise neurosurgical therapy (reconstruction of carotid artery, evacuation of intracerebral clot). But in the ordinary care of the stroke patient, arteriography plays a very minor role, and apart from ruptured saccular aneurysm is contraindicated as subjecting the patient to an unnecessary risk and expense. Compression of the common carotid artery in the neck as a test of the patency of the vessel on the opposite side with the production of unconsciousness and/or seizures if the latter is obstructed appears to be a relatively safe maneuver, but rarely will it be crucial in deciding the course of therapy; therefore its use is not advised except in special circumstances. Tilting of the patient on a tilt table with concomitant electroencephalographic recording has provided useful experimental data, but again as a routine diagnostic procedure its value is limited since it may provide both false-positive and false-negative information and the final decision as to diagnosis and treatment will be determined on other information (chiefly an analysis of the clinical data).

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## TREATMENT

The treatment of cerebrovascular diseases and strokes may be divided into four parts: (1) general medical management in the acute phase; (2) measures to arrest the pathologic process and restore the integrity of damaged brain tissue; (3) physical therapy and rehabilitation; and (4) preventive measures against strokes and vascular disease.

*General Medical Management.*—The general medical management in the acute phase is the care of the comatose or helpless patient, and it is not intended to deal at length with that broad subject here. Maintenance of the airway is of first importance, a tracheostomy being performed promptly if suctioning of the pharyngeal secretion becomes necessary in the stuporous patient. Intravenous fluid for the first 2 or 3 days followed by transnasal stomach tube feedings is the best means of nourishment remembering that hypotonic solutions given too quickly intravenously aggravate brain swelling. If an indwelling urinary catheter is used, daily irrigations must be carried out. The catheter is changed every 5 to 7 days, the urine is maintained in an acid condition and antibiotics are employed as need arises. Other measures include elastic stockings, correction of cardiac failure, possibly oxygen therapy, and routine anticonvulsants, Dilantin 0.1 Gm. three times a day. Fecal impaction must be suspected if patient is incontinent of small amounts of feces frequently.

*Measures to Arrest Pathologic Process and Restore Integrity of Damaged Brain Tissue.—*

*Cerebral thrombosis and embolism:* The methods used in recent years include:

1. Cervical sympathetic block: This procedure has fallen into disuse since careful clinical studies failed to confirm the initial reports of its beneficial effect.

2. Cerebral vasodilators: Despite experimental evidence that these agents increase the cerebral blood flow, they have not proved beneficial in careful studies in human stroke cases. This is true of 5 per cent carbon dioxide, nicotinic acid, Priscoline, alcohol, and papaverine. A few clinical trials have shown that histamine, aminophylline, and intra-arterial papaverine have some merit, but further investigation is needed.

3. Medical measures to increase the blood supply to the brain: Clinical observations indicate that strokes and ischemic attacks in many cases develop when the patient gets up from his bed, particularly in the morning or postoperatively. In the upright position the cerebral circulation falls, and for this reason it is recommended that patients with a stroke as the result of ischemic infarction should remain horizontal in bed for 7 to 10 days initially and that when ambulation starts special attention should be given to maintenance of the systemic circulation (the patient must avoid standing quietly for prolonged periods, must sit with feet up, etc.). In stroke cases it is of great importance that the systemic blood pressure be maintained (correction of blood loss, use of Levophed in myocardial infarction with vascular collapse, avoidance of autonomic blocking agents, etc.). Injections of epinephrine have been recommended as a means of raising the systemic blood pressure above the usual levels and thus enhancing cerebral blood flow. This could be a beneficial procedure, but a systematic trial in thrombotic cases has not been undertaken. Anemia must be corrected.

4. Surgical measures: Recently a few surgeons have undertaken to relieve carotid artery obstruction surgically and restore normal blood flow. The procedures used include carotid thromboendarterectomy, resection of the carotid bifurcation with either a direct end-to-end anastomosis or insertion of a graft and the use of loops of arterial graft or plastic conduit. Some of these operations were performed in cases in which a stroke had recently developed. In others, they were carried out at the stage of prodromal transient ischemic attacks or early in the course of thrombosis-in-evolution. Only a minority of cases will be candidates for this type of surgery, because the thrombus usually extends from the region of the carotid sinus upward into the inaccessible reaches of the internal carotid artery. There can be no doubt that restitution of the carotid circulation is a highly desirable goal, although the accomplished infarction will not be remedied. It might be argued that nonetheless extension of the infarction will be prevented and the intracranial circulation will be protected in case occlusion of the opposite carotid takes place. Before operation is considered on these grounds, it will have to be shown that the procedure is not dangerous to the patient, will not aggravate his neurologic deficit, and will be effective both immediately and for a relatively long period (3 to 5 years). Embolectomy should be feasible in cases in which the embolus is arrested at the carotid bifurcation.

In regard to the use of surgical measures at the stage of transient ischemic attacks or early in thrombosis-in-evolution, the prospective benefit is much greater, but the danger that surgery will transform a relatively minor deficit into a major catastrophe must be reckoned with. This type of surgery must be regarded as still at the experimental stage, and it is to be hoped that a safe,

effective, durable surgical procedure will be evolved. It is not sufficient that the surgeon report his good results at the end of a few months in a group of patients whose vascular diagnosis has not always been precisely determined.

*Intracerebral hemorrhage and ruptured saccular aneurysm:* Medical measures have not been methodically exploited in these conditions. The possibility of using intermittent carotid compression in an attempt at arresting intracranial bleeding comes to mind especially in the former type where the first hemorrhage is fatal in a high percentage of cases. In regard to restoring the integrity of damaged brain tissue, the only possible procedure is evacuation of the clot within the hemisphere. There have been sporadic attempts to treat intracerebral hemorrhage by operating in the acute stage, and results have not been promising. It formerly was said that all of these patients might as well be operated on because, since all patients died anyway no harm could be done, and some benefit might accrue. This viewpoint is hardly correct, for in a personal series it was found that the patient survived intracerebral hemorrhage with bloody spinal fluid in some 25 per cent of cases. If surgery is contemplated, the possibility of such a satisfactory course must be kept in mind. Surgical removal of the intracerebral clot in cases of saccular aneurysm and angioma is successfully undertaken in many cases, and the reason for success here and failure in the hypertensive group is not clear.

*Physical Therapy and Rehabilitation.—*

Beginning within a day or two the joints of the paralyzed limbs should be passively carried through a full range of motion 20 to 50 times a day. Contracture shortening must be avoided, especially at the shoulder, elbow, and ankle. The patient can be placed in a chair after 2 weeks or so, depending on the severity of the illness. Nearly all hemiplegics can learn to walk again to some extent, usually within a 3- to 6-month period. A long or short leg brace is often required. Speech therapy is of questionable value but should be tried. At least it is of value psychologically to patient and family. Physical therapy seems not to benefit patients with cerebellar ataxia. As the hemiplegic patient improves and if the mentality is preserved, instruction in the activities of daily living will assist him in becoming more independent in the home.

*Preventive Measures Against Strokes and Vascular Disease.—*

*Cerebral thrombosis:* Once ischemic infarction has occurred, no therapy so far devised is of any value in restoring function. There is thus no need to emphasize that prevention is the most important category of therapy. Preventive measures in cerebral thrombosis may be divided into special and general.

SPECIAL.—1. Prevention of a thrombotic stroke of which there has been a warning in the form of one or more transient ischemic attacks: Many different therapies have been recommended for these attacks, but most have failed when carefully tested, including papaverine and phenobarbital, cervical sympathectomy, nicotinic acid, aminophyllin, and breathing 5 per cent carbon dioxide in air. In recent years, anticoagulant therapy has shown promise of being an effective measure, although not yet subjected to a controlled trial. Anticoagulants appear both to prevent ischemic episodes and to postpone indefinitely the

arrival of an impending stroke whether the carotid or basilar artery is involved. Surgical reconstruction of the carotid artery in the neck has been referred to on page 442.

2. Halting the advance of a progressive thrombotic stroke (stroke-in-evolution): This problem is closely allied to the one just discussed, and the same measures have been used here. Only anticoagulant therapy appears to bring significantly beneficial results.

In trying to decide whether or not anticoagulant therapy is indicated, one faces a crucial question in cerebral thrombosis: Where in the course of a stroke does the patient stand when he is first examined? Will there be further transient ischemic attacks? Will the present deficit worsen, or will the patient recover spontaneously? Unfortunately, no answers to these questions have yet been formulated. We have all seen cases in which only one warning episode preceded the sudden development of a severe disability. Probably every physician has been embarassed to find that what appeared to be a rather innocent looking mild stroke has turned abruptly into a major catastrophe.

3. Prevention of repeated strokes: Not infrequently, one encounters patients in whom several separate, usually small thrombotic strokes occur within a period of several months. Hypertension is usually present. Thus far, anticoagulant therapy is the only measure recommended for the prevention of the recurrences, but its real value has yet to be assessed.

4. Prevention of a stroke by avoiding situations in which strokes are liable to occur: Particular care should be taken to maintain the systemic blood pressure, oxygenation, and intracranial blood flow during surgical procedures, especially in elderly patients. Hypotensive agents, whether given therapeutically or for diagnostic purposes should be administered with great care. In the elderly patient in whom deep sleep might help to precipitate cerebral ischemia, oversedation should be avoided. Systemic hypotension, severe anemia, and polycythemia should be treated promptly.

ANTICOAGULANT THERAPY.—Anticoagulants are indicated when transient ischemic attacks are becoming worse, more numerous, or lasting longer. They are especially needed if a transient ischemic attack does not reverse itself completely but leaves a neurologic deficit. When a single transient ischemic episode has occurred, the possibility that cerebral embolism is responsible must be kept in mind. Anticoagulants are indicated when a stroke is developing in a stepwise or fluctuating manner over a period of hours or days. When a "partial stroke" has taken place, that is, the neurologic deficit present is less than might be expected from total infarction of the territory whose artery is occluded, anticoagulants should be administered to prevent a further increment of paralysis (this is actually a stroke-in-evolution in which progression is not obvious because of a delay in worsening after the first part of the stroke has occurred). It would be preferable to select the candidates for anticoagulant therapy and spare patients as far as possible the expense and nuisance of taking anticoagulant drugs but as mentioned above, no rules have yet been laid down that will enable one to distinguish those patients who will fare well from those who are destined to become paralyzed.

For anticoagulation purposes, a drug of the coumarin family (Dicumarol, Coumadin, etc.) is given alone or in combination with heparin. If an anticoagulant effect is urgently required as in thrombosis-in-evolution or when ischemic attacks are occurring in rapid sequence (more than one per day) heparin is administered intravenously in doses of 50 to 75 mg. every 3 to 5 hours (usually 50 mg. every 4 hours) until Dicumarol becomes effective. Clotting times may be determined 3½ hours after the initial dose and then daily thereafter just before one of the scheduled doses, but in many centers even this amount of control has been abandoned.

It is well worth emphasizing that routes other than the intravenous are not adequate when the patient is in the throes of an evolving stroke.

The prothrombin activity is maintained at about 15 per cent of normal, and the level is determined every 7 to 10 days for long-term anticoagulant therapy. Therapy can be prolonged for months and years, and only occasionally is it necessary to interrupt treatment permanently because of hemorrhagic complications. Overdosage may result in bleeding from the kidney, nose, bowel, skin, or muscle, and although these accidents are not serious vitamin $K_1$ should be administered immediately; the practice of stopping the drug and waiting for the prothrombin activity to fall spontaneously usually results in bleeding for several days.

The use of anticoagulant drugs makes an accurate clinical diagnosis imperative. Intracranial hemorrhage must be especially ruled out, chiefly by relying on examination of the spinal fluid. Anticoagulant drugs are absolutely contraindicated if there is a focus of active bleeding anywhere in the body. It is wise to examine the stool for blood before starting therapy. Although data on the danger of anticoagulant therapy in the presence of hypertension are not conclusive, hypertension appears not to be a contraindication even if excessively high levels are present, but in the latter circumstance, an attempt is made to lower the blood pressure starting two weeks after the thrombotic stroke. This liberal viewpoint may need amending as experience is gathered. Anticoagulants are contraindicated in lupus erythematosus.

In regard to the length of time a patient need be maintained on anticoagulants, no reliable rules have been set down as yet. In the most serious cases they may be administered indefinitely, or at least for 6 to 12 months; in milder cases, the drug is stopped after 6 to 8 weeks, the patient is asked to report any untoward signs immediately, and heparin is administered intravenously if the need arises.

GENERAL.—Anticoagulant therapy constitutes but a delaying action in the prevention of strokes, and the ultimate solution lies in the more fundamental fields of atherosclerosis and hypertension. The latter will not be discussed here except to note that lowering the blood pressure rarely precipitates infarction unless there are drastic swings to hypotensive levels as in the case of blocking agents, and occasionally with reserpine. Hypertension is a most serious aggravant of atherosclerosis, and where a proclivity to atherosclerosis exists, the blood pressure should be reduced to normal if at all possible.

In regard to atherosclerosis, patients are given a diet containing 25 to 40 Gm. of fat per day, the total calories depending on whether or not weight reduction is desired. Patients are advised to reduce their body weight to normal range. Smoking cigarettes is forbidden. Unsaturated fatty acid supplements may be tried.

*Cerebral embolism:* Most aspects of the therapy of cerebral embolism have been referred to under cerebral thrombosis, namely treatment in the acute stage, measures to restore the damaged tissue, and physical therapy. There remains for discussion here the prevention of cerebral embolism. It is widely accepted that anticoagulants reduce the incidence of embolism from the heart in cases of atrial fibrillation and myocardial infarction, and although these data do not have the desired statistical validity, it has become common practice to administer anticoagulants on a long-term basis to prevent the occurrence and recurrence of embolism. All cases of myocardial infarction including the "good risk" category should be considered for anticoagulant therapy. After cerebral embolism has occurred, the question arises as to the necessity of delaying anticoagulant therapy for several days to avoid precipitating bleeding into a hemorrhagic infarct. Lumbar puncture should always be performed first to rule out gross hemorrhage from the infarct. If the spinal fluid is clear, anticoagulant therapy can probably be safely given without delay; as already mentioned at the Massachusetts General Hospital, we have not yet encountered a case pathologically in which anticoagulants have increased the degree of hemorrhage within a hemorrhagic infarct. After embolism has once occurred, recurrence may come in a matter of hours or days, and it is dangerous to delay therapy.

Valvoplasty and amputation of the auricular appendage have substantially reduced the incidence of embolism in rheumatic heart disease.

*Hypertensive intracerebral hemorrhage:* The prevention of cerebral hemorrhage is clearly the alleviation or prevention of arterial hypertension.

*Ruptured saccular aneurysm:* The principal aim in the therapy of saccular aneurysm is the prevention of recurrence of bleeding. Re-bleeding may occur any time, even the first few days after the original hemorrhage, but surgery in the early period after rupture carries with it a high mortality and morbidity. Whether surgery should be undertaken and if so, when, depends on several factors, the age of the patient, the degree of coma, the disturbance of vital functions, the presence of a serious focal neurologic deficit, etc. The bolder surgeons exemplified by Botterell operate early under hypothermia, attacking the aneurysm directly, intracranially, and achieve what appears to be a significant improvement in the outlook of these patients, although no data from a comparable group of medically treated patients with arteriograms are available for comparison. Others prefer, if possible, to use ligation of the common carotid artery in the neck reserving the intracranial approach for cases in which either the aneurysm lies on the anterior communicating artery or cases in which ligation of the carotid artery is not tolerated. Recent data indicate that the incidence of recurrence of bleeding is insignificant after carotid ligation and that ligation seems not to prejudice the cerebral circulation as determined by follow-up periods as long as 10 years. There can be no question that ligation of a main arterial trunk

in the neck in the treatment of a small focal intracranial lesion is an undesirable procedure, but intracranial operation is a most hazardous undertaking except in the hands of the most experienced experts in this field.

SUMMARY

A brief review of some of the main features of cerebrovascular diseases has been presented. The rules formulated here have proved of great value in the day-to-day management of stroke cases at the Massachusetts General Hospital. No doubt, some of the observations and claims will need revision as studies proceed.

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# EPILEPSY

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EPILEPSY is a disease as old as the writings of Hippocrates, shrouded in many misconceptions, and still defying accurate pathophysiologic description. It is not a single entity, but encompasses the "seizure disorders."

In the latter half of the nineteenth century, Hughlings Jackson[1] presented us with our first understanding of focal seizures and with the classical physiologic definition of epilepsy: "Epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of gray matter . . . it occurs with all sorts of conditions of ill health at all ages and under innumerable circumstances."

Clinically it is difficult to define the convulsive disorders in terms which would cover their manifold features. One definition is that a patient has a convulsive disorder or epilepsy when he is subject to transient, periodic attacks of change of the state of consciousness which may or may not be accompanied by motor and/or sensory phenomena. This definition is inadequate because the motor and sensory phenomena may occur without any obvious disturbance of consciousness, just as the disturbance of consciousness may occur without any motor or sensory phenomena.

The incidence of epilepsy is unknown; the figures given vary from 0.5 to 1.5 per cent of the population, so that there are probably well over 1.5 million Americans to whom this diagnosis might be applied.

## PATHOPHYSIOLOGY

Our lack of an adequate scientific definition of epilepsy reflects the continuing mystery of its pathophysiology. Jackson[1] considered "that the term epilepsy should be degraded to stand for our knowledge, or rather for our ignorance, of the various permanent and temporary conditions of nerve tissue in functional divisions, or perhaps in nutritive regions, which conditions cause or prevent temporary failures or losses of function." Convulsive seizures may be produced in normal individuals by the injection of various substances such as Metrazol and by electrical stimulation. It could be said that a convulsion is the normal motor response of the nervous system to overwhelming stimuli. Electrical stimulation reveals marked threshold excitability differences between individuals and even varia-

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tions in the same individual. The problem of inherent lowered thresholds in the epileptic brain and what predisposes this brain to autostimulation remains unanswered.

Disturbances of mineral, glucose, water, and other metabolisms, as well as anoxemia, may be associated with convulsions, but none of these disturbances are present in any significant number of patients with epilepsy. Organic brain lesions are associated with a high seizure incidence but, again, in the majority of patients with seizures, evidence of gross damage to the brain is lacking. A static state of brain damage, when present, cannot of itself account for paroxysmal seizure activity. An undue susceptibility of the relatively normal brain in the neighborhood of the destroyed or damaged nervous tissue to various stimuli or metabolic disturbances might explain the high incidence of seizures in patients with organic lesions in the nervous system. Prenatal and paranatal factors, producing initial subclinical brain damage, are of undoubted importance, but far from universal in their occurrence in the epileptic population, either as to history or pathologic confirmation. The brains of epileptics reveal no consistent specific changes. Many organic lesions of the nervous system that have been associated with a convulsive disorder also occur in patients who have never had a seizure. Nonspecific pathologic findings, in terms of sclerosis of Ammon's horn, minute areas of cortical cellular loss, changes in the anatomy of the meninges and ventricles, are more likely the result rather than the cause of convulsions.

The role of hereditary factors in the occurrence of epilepsy has not been fully elucidated. In the study of twins affected by seizures, Lennox[2] has shown that in twin pairs, without prior recorded brain damage, both were epileptic in a majority of identical pairs. He further noted seven times the incidence of epilepsy in the near relatives of patients with "idiopathic seizures." A family history of epilepsy in patients whose seizures developed following damage to the brain is three times the expected incidence in the total population.

Studies of prenatal and paranatal factors, however, reveal significantly more abnormalities in epileptic children during these periods than in matched controls. The abnormalities bear no relationship to parental seizures, seizure type, or electroencephalographic pattern. A tendency to varied difficulties of pregnancy and labor may represent a "continuum of reproductive causality" and be of more significance than primary genetic factors.[3,4]

Thomas Willis in the eighteenth century likened seizures to the explosion of a charge of gunpowder and stated that the final cause of epilepsy is chemical. This latter concept represents the current frontier of research and understanding in the pathophysiology of epilepsy. Based on chemical analysis, Tower[5] demonstrated that excised human epileptogenic cortex had decreased amounts of bound acetylcholine, but that if glutamine or asparagin were added bound acetylcholine levels returned toward normal. It was also demonstrated that animals given high dosages of phenobarbital and diphenylhydantoin produced significantly greater amounts of bound acetylcholine than untreated controls. Pappius and Elliott,[6] however, repeating these experiments, have failed to obtain similar results and find amounts of bound acetylcholine in epileptogenic brain tissue not significantly different from those in nonepileptogenic controls. Amino acid

metabolism and its related compounds undoubtedly play a role, not as yet clearly defined, in the seizure process. Naturally occurring brain amino acids have been shown to inhibit synaptic transmission.[7] One of the most potent of such inhibitors, gamma-aminobutyric acid, has, in animals, been shown to increase in the presence of diphenylhydantoin.[8] Pyridoxine deficiency seizures are well known. In its coenzyme form, this substance catalyses most reactions of amino acids. Its lack reduces the enzymes related to the production of gamma-aminobutyric acid.

It is currently postulated that the balance between the gamma-aminobutyric acid and acetylcholine systems may be the prime factor in altered excitability states of the brain and in such abnormalities as epilepsy. Whatever decreases gamma-aminobutyric acid and therefore neuron inhibition will result in failure to modify neuron excitation and produce an indiscriminate spread of electrical impulses with resultant seizures.[9]

Studies indicating increased amounts of extracellular water and electrolytes in epileptics are of interest but of uncertain significance and seemingly unrelated to the mode of action of the effective anticonvulsants.[10,11]

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## CLINICAL SYMPTOMATOLOGY

Seizures have been conventionally subdivided into symptomatic or acquired epilepsy, implying demonstrable organic or metabolic disturbances as the underlying basis for the seizures and idiopathic epilepsy when no such lesions or defects can be demonstrated. This is not wholly accurate, for it presumes that seizures in patients with symptomatic epilepsy are due solely to organic lesions and that there is no pathology in the patient with so-called idiopathic epilepsy. This latter assumpton is not justified, for all that we can say is that by the methods now available there is no demonstrable pathology. Patients initially considered to have an idiopathic convulsive disorder, may, as additional manifestations of their cerebral lesion become evident, have to be placed in the symptomatic group. This may be particularly true of some patients with vascular anomalies of the brain, or with slow growing cerebral neoplasm. It is extremely important from a therapeutic standpoint to classify convulsive manifestations accurately as to seizure type, although on occasion this may be difficult.

The physical manifestations which occur during the attacks may generally be regarded in five groups: (1) grand mal, major or generalized seizures; (2) petit mal or minor attacks; (3) minor motor attacks; (4) psychomotor attacks and epileptic equivalents; and (5) focal seizures. Advances in cortical electrophysiology, and delineation of the presumed site of abnormal discharges have increased our knowledge and understanding of the seizure process but not our concepts of therapy.[12]

*Grand Mal Seizures.*—Grand mal seizures are the most common type of convulsive phenomena, occurring in approximately 90 per cent of patients either alone or in combination with other forms. Typical episodes consist of an aura, epileptic cry, loss of consciousness, tonic and clonic phases, and a postseizure state. The convulsive stage may be associated with tongue biting, urine or fecal incontinence, and occasionally ejaculation. Respirations often cease with

resultant cyanosis during maximum tonicity, only to become irregular and stertorous as the seizure merges into its clonic phase. The aura forms an integral part of the attack and occurs in almost 50 per cent of patients experiencing grand mal episodes. It may be no more than an ill-defined sensation of fear, vertigo, or weakness. In certain cases, the aura may be indicative of a definite epileptogenic focus and represent the only clinical manifestation of a focal cortical lesion. In the postseizure state the patient may be transiently confused, complain of headache, be drowsy, or actually sleep for several hours. The frequency and severity of these attacks are highly variable. The episode may last less than a minute or more than 10 minutes, and it may occur many times a day or as infrequently as once in several years. Abortive forms are common, particularly when partial control has been obtained with anticonvulsant drugs. The attacks may be predominantly nocturnal during sleep but are usually spread throughout the entire 24 hours.

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*Petit Mal Seizures.*—Petit mal seizures are not associated with an aura; they are very brief in duration (5 to 30 seconds) and are not followed by a postseizure state. They are most common in childhood and are rarely initially manifest in the adult. These spells are characterized by a transient clouding of consciousness with little or no bodily manifestations of change. Outward evidence may be only a staring expression of the eyes, blinking, or minor movements of head or extremities. The episodes tend to occur many times per day. The attack may be so mild that the patient is unaware of any change in consciousness. Petit mal episodes may be associated with loss of urinary sphincter control and tend to be more common in the morning.

It is important from a therapeutic standpoint to differentiate petit mal episodes clearly from other minor seizure phenomena. Electroencephalographically these patients present with a characteristic pattern of three per second slow wave activity associated with fast spikes, occurring bilaterally and synchronously in all leads. The true petit mal rhythm has only rarely been seen following lesions acquired more than a short period after birth, and it is taken as certain evidence of "idiopathic epilepsy."

*Minor Motor Seizures.*—Seizures which resemble petit mal (in that they are very brief) and occur with great frequency and without postseizure phenomena may be considered minor motor episodes. Lennox included akinetic seizures (sudden toneless episodes with falling) and myoclonic jerks (sudden involuntary muscular contractions of the trunk or limbs) with petit mal because of their similar electroencephalographic pattern. Akinetic and myoclonic seizures, however, are quite refractory to those drugs generally effective in pure petit mal and not always associated with a typical wave and spike electroencephalogram. The akinetic fall episodes are usually of such brief duration that the patient immediately arises and has no subjective or objective evidence of loss of consciousness. Both akinetic and myoclonic seizure phenomena may occur in patients with petit mal but are also seen in patients whose seizures are of the grand mal type.

In infants under 1 year of age there may be massive myoclonic episodes that have been termed infantile spasms. These usually occur many times a day and

last less than 10 seconds. This form of myoclonic phenomenon tends to be associated with brain damage and mental retardation.[13]

Minor episodes characterized by transient loss of consciousness without fall or convulsive phenomena, occurring less frequently than petit mal episodes, often associated with postseizure symptoms and not with a classic petit mal EEG, may be confused with petit mal seizures. These episodes are usually fragments of grand mal attacks and are more likely to occur in patients whose grand mal episodes have been partially controlled by drug therapy.

*Psychomotor Seizures.*—Psychomotor episodes are more common in adults but do occur in children and are often confused with petit mal. Their manifestations may on occasion be bizarre to the point of being considered hysterical or psychotic symptoms. The episodes last longer than the petit mal attacks and are usually followed by postseizure amnesia. During the episode, one may note purposeful motor and mental activity that is incongruous for the immediate situation. Movements noted may be lip smacking, fumbling with clothes, or disrobing. Assaultive and destructive behavior is rare, but the patients commonly resist vigorously any help offered during the attack. In psychomotor episodes the electroencephalographic abnormality may be nonspecific, but in a high percentage of cases the tracing is associated with focal abnormalities of either or both anterior temporal lobes. The attacks may be associated with an aura indicating focal temporal lobe phenomena but may emanate from other areas as well.

Many ill-defined paroxysmal episodes have been frequently considered "equivalent" convulsive phenomena. Paroxysmal abdominal pain, occurring primarily in children, may on occasion be a clinical seizure variant termed abdominal epilepsy. If associated with an abnormal electroencephalogram, particularly during the pain episodes, this diagnosis may be considered.[14] These patients may or may not respond to anticonvulsant therapy. Paroxysmal nausea, vertigo, headache, nightmares, and personality changes may also represent epileptic equivalents. Care must be taken not to consider symptoms indiscriminately as epileptic equivalents on the basis of EEG abnormalities that may be unrelated to the clinical syndrome presented.[15]

*Focal Seizures.*—Focal seizures are characterized by motor, sensory, or combined phenomena of various types indicating their cerebral site of origin. They may remain localized or progress to a generalized seizure episode with loss of consciousness. The progression of seizure phenomena from one part in a sequence of "march" consistent with contiguous areas of cortical representation is referred to as a Jacksonian episode. Focal seizures must always be considered as indicative of gross organic brain pathology. Lesions responsible for such seizures may, however, be only microscopic and are often the result of birth injury, infection, or trauma. Focal seizures are not pathognomonic of brain tumors.

*Treatment.*—While it is true we still have a great deal to learn about the cause and mechanism of seizures, advances in the drug therapy of convulsive disorders has made it possible to control or reduce the frequency of attacks in approximately 80 per cent of cases.[16]

The approach to therapy has many aspects and encompasses three main goals: (1) definition of primary etiologic factors, (2) modification of secondary factors in terms of general physical and mental hygiene, and (3) medical therapy.

Primary and precipitating factors are defined and removed where possible. This applies mainly to the symptomatic convulsive disorders and encompasses the fields of neurosurgery in terms of brain tumor, cerebral abscesses, and cortical scars. It also includes consideration of acute or chronic infectious conditions and metabolic disturbances such as spontaneous hypoglycemia and hypoparathyroidism.

The most important factors in terms of general health are moderation and regularity. One must attempt to promote normal physical activity commensurate the patient's age, general condition, and state in life; a balanced dietary program, and regular sleep habits. The moderate occasional social use of alcoholic beverages by the adult is not necessarily contraindicated except in cases where such usage seems to be related to breaks in medication regimen or increased seizure rate. Adequate socioeconomic adjustment of the patient cannot be obtained via purely medical or surgical management. He cannot be treated in the framework of a physiologic vacuum, consisting purely of seizure discharges. Therapy is inseparably related to a proper intellectual and emotional awareness by the patient, his family, associates, employers, and the community at large as to the meaning of a convulsive disorder and the individual's total potential. Many patients whose adjustment would be otherwise satisfactory are the victims of an overprotected, excessively restricted, fearful, ashamed constellation of acts and emotions that cripple them in spite of the relative adequacy of seizure control. There is no epileptic personality; only the inherent personality of the individual and its modification by the attitude of others and himself. The most effective form of emotional approach remains the demonstration to the patient that the seizure phenomena can be adequately controlled with anticonvulsant medication. The patient, his family, and associates must be educated early in the course of therapy in order to negate the misconceptions and pseudoscientific dogma prevalent in lay and medical populations. It must be pointed out that a convulsive disorder is not synonymous with mental retardation and that the condition is not incompatible with intellectual superiority.[17] The patient must be treated with an attitude of expectancy, in terms of its being the natural anticipated course of events that he lead a normal, natural life without undue restrictions, be maintained in school, considered employable, and not barred from marriage and a family. The concept that the epileptic cannot do this or that, that he is unsuitable for this industry or that profession, has become so rooted in the minds of many individuals that they believe it to be true, and by such restrictive labeling they have "convinced" a large segment of our convulsive population that such is also actually the case. The largest sociopsychologic problem facing the epileptic remains that of employment. Objective evaluation does not justify the concept of a high industrial accident rate among epileptics.[18]

The only effective way at present of controlling seizures in the majority of cases is by the use of anticonvulsant drugs. The many medical therapies of antiquity have given way to a current rational pharmacologic approach that had

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its beginnings in the nineteenth century.[19] It has progressed from Locock's use of bromides (1857) to the addition of phenobarbital (1912), Dilantin (1938), and Tridione (1946).

Drug therapy in any patient must be highly individualized. There is actually no one dosage; within the limits of side effects and toxicity the dosage is "enough." Drug choice depends on seizure type. The most common causes for the failure of treatment are: improper classification of seizure type, failure to recognize a progressive neurologic disease, failure to use proper drugs, failure to administer proper dosage, frequent shifting of drugs, premature withdrawal of drugs, poor indoctrination of patients, and lack of recognition of social and economic needs of patients.[20] The greatest single number of failures is related to failure to administer the amount of drug required and failure to use two or more drugs in combination. The patient should be started on a small or moderate dosage of the drug which is considered to be suitable, with gradual increase of dosage at suitable intervals until the seizures are controlled or the appearance of minor toxic symptoms make further additions inadvisable. If more than minor toxic phenomena develop, the medication should be withdrawn and another substituted. When the drug used initially is well tolerated but is not capable of controlling the seizures, another compound should be added. Usually, large doses of each drug are needed when two or more drugs are utilized.

The drugs commonly used in the treatment of patients with convulsive seizures are the barbiturates, hydantoins, oxazolidinediones, and to a lesser extent the acetylureas, succinamides, acetazolamides, and bromides. Table I lists compounds that are commercially available.

In all types of seizures, except petit mal, the initial drugs of choice are diphenylhydantoin sodium and/or phenobarbital. These drugs have been shown to have a high therapeutic efficacy, minimum untoward side effects, and are commonly regarded as standard anticonvulsant compounds. When toxic reactions to these drugs occur, they are rarely serious and are reversible when administration of the drug is discontinued or the dosage is adjusted. In patients with infrequent seizures (less than one a year), phenobarbital may prove effective by itself and in such instances usually is the drug of choice. In patients with more frequent attacks, diphenylhydantoin sodium usually is preferred as the initial compound with phenobarbital being added at such time as diphenylhydantoin sodium proves ineffective as the sole agent for seizure control. When both are incapable of producing desired results, addition of other drugs such as Mesantoin, Mebaral, or Mysoline can be tried.

Tridione, Paradione, Milontin, and Celontin are the only drugs that have any appreciable influence on the frequency of petit mal attacks. These anticonvulsants, with the exception of Celontin, are not effective against other seizure types and are felt by some to increase major seizure phenomena when such coexists. If the patient has a combination of seizure types, therapy must be combined with diphenylhydantoin or phenobarbital. Minor motor seizures are the most difficult of all attacks to control by anticonvulsant drugs. They must be carefully distinguished from petit mal episodes. Dr. Lennox, considering these seizures to be a segment of the petit mal triad has recommended the petit mal drugs. Only occasionally, however, are these compounds effective.

When an anticonvulsant or a combination of anticonvulsants is found to be effective, it should be maintained. The pressures from the patient and others to utilize newer drugs should be reserved for those resistant to therapy with adequate doses of well-established compounds.

TABLE I. COMMERCIALLY AVAILABLE ANTICONVULSANTS

*Barbituric acid derivatives*
- Phenobarbital
- Mephobarbital (Mebaral)
- Metharbital (Geminol)
- Primidone (Mysoline)

*Hydantoin derivatives*
- Diphenylhydantoin sodium (Dilantin)
- Methylphenylethylhydantoin (Mesantoin)
- Ethotoin (Peganone)

*Phenylacetylurea derivative*
- Phenacemide (Phenurone)

*Bromides*
- Sodium or potassium bromide

*Oxazolidine derivatives*
- Trimethadione (Tridione)
- Paramethadione (Paradione)

*Succinamide derivatives*
- Phensuximide (Milontin)
- Methsuximide (Celontin)

*Carbonic anhydrase inhibitor*
- Acetazoleamide (Diamox)

*Amphetamines*
- Amphetamine sulphate (Benzedrine)
- Dextro amphetamine sulphate (Dexedrine)

*Phenobarbital.*—The initial dose for the adult is 0.1 Gm. usually given at bedtime. If indicated, this dose is gradually increased at suitable intervals until the patient is taking as much as 0.3 to 0.4 Gm. a day. If this amount fails to control seizures, it is doubtful that further increases will be of value. Initial dosages in children are proportional to weight, but they are often able to tolerate and require almost as large a dose as adults. It is therefore advisable to give children over 6 years of age the minimal dose of 0.1 Gm. a day. The toxic side effects of Phenobarbital are seldom serious. Drowsiness and lethargy are common at the onset of treatment and at higher dosage levels but in most patients disappear with continued therapy. If they do not, the use of amphetamine sulphate (5 to 20 mg. daily) or other suitable amphetamine derivatives can be tried, being given

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in single or divided doses in the morning or early afternoon. Less than 1 per cent of patients who receive phenobarbital develop an allergic dermatitis of a scarlatiniform or morbilliform nature; the drug should be discontinued until the rash disappears. There is no time limit to this cutaneous toxic manifestation, and it may occur within weeks to years of drug utilization. If the rash recurs on subsequent administration, the further use of phenobarbital is contraindicated because of the danger of an exfoliative dermatitis. Other toxic manifestations such as ataxic gait, tremors, nystagmus, vertigo, blurring of vision, and extreme drowsiness may occur with higher dosage but seldom with amounts less than 0.3 Gm. per day.

*Diphenylhydantoin sodium* (*Dilantin*): Dilantin is a highly effective anticonvulsant and has little or no sedative effect. Initial adult dosage is 0.1 Gm. given 2 to 3 times a day. Dosage may be increased by 0.1 Gm. at weekly intervals until optimal effect is obtained. It may be increased to a 0.4-0.6 Gm. level and given as a single daily dose or in divided amounts during the day, preferably after meals. The optimum level of tolerance is in many patients quite critical. The difference between seizure control dose and toxic dose may be as little as 50 mg. The initial dose in children over 6 years of age is 0.1 Gm. twice daily and in younger children 0.03 Gm. 3 times a day.

Many minor toxic manifestations may occur. Gastric distress and nausea may be noted with initial doses. This is obviated by taking the drug at meal time or with sodum bicarbonate. Transient nervousness, sleeplessness, and a feeling of unsteadiness are occasionally encountered during the first few days of treatment but subside with continued use. Nystagmus develops in many patients taking Dilantin but in itself does not constitute an indication for cessation of the drug or reduction in dosage. Hypertrophy of the gums is quite annoying and is most common in children. It varies from a slight swelling to marked hyperplasia almost totally covering the teeth. This can to some degree be retarded by massaging the gums daily and by good oral hygiene. This response bears no relationship to dosage and is rarely seen in the first few months of treatment. When excessive hyperplasia occurs, surgical excision is indicated. Hirsutism may be noted, usually in younger patients in the adolescent and preadolescent age group. This is particularly disturbing in girls, but in most instances is mild. It may not disappear with the elimination of therapy, and unless it is extremely marked and progressive it should not warrant discontinuance of the drug. When nystagmus occurs in association with ataxia and diplopia, reduction of the dose is indicated. Reducing the dose by 0.1 Gm. will alleviate these symptoms if they are mild. If they are more intense, reducing the dose to one-half for 3 to 5 days will be necessary. With subsidence of symptoms the dosage may be slowly increased to a level just below that at which toxic reactions previously presented.

Major allergic phenomena such as fever, polyarthropathy, and skin eruptions are rare, but they are causes for change in anticonvulsant medication when they occur. The skin eruptions seen with diphenylhydantoin sodium occur in 5 to 10 per cent of patients and are of two varieties. The first is an acute generalized morbilliform eruption with or without a temperature elevation, usually oc-

curring about 2 weeks after treatment has begun. Discontinuing administration of the drug results in complete alleviation of this toxic manifestation. The second type of eruption is an exfoliative dermatitis, occurring any time during the course of treatment. Both of these cutaneous manifestations subside when the drug is withdrawn. Further use of the drug may be attempted beginning with smaller doses and increasing at smaller increments, but the chances of success are small.

It must be remembered that diphenylhydantoin sodium requires 48 to 72 hours of administration to reach a level of therapeutic effectiveness. Other drugs may be utilized alone or in combination with diphenylhydantoin sodium or phenobarbital should the latter compounds prove to be ineffective or to have too many undesirable side effects.[21]

*Methylphenylethylhydantoin* (*Mesantoin*): Mesantoin is another hydantoin derivative closely related to Dilantin and is an effective anticonvulsant. Relatively larger doses are required, 0.4-1 Gm. daily. The toxic effects are similar to those of diphenylhydantoin sodium, but Mesantoin does not produce gum hypertrophy and has considerably more sedative effect. Its most serious toxicity is the production of blood dyscrasias (agranulocytosis, pancytopenia, and aplastic anemia) which may be fatal. This commonly occurs during the first few months of treatment but may occur at any time in the course of therapy. Because of this the drug must be used with extreme care and only when relatively nontoxic compounds such as phenobarbital and Dilantin have proved ineffective. Patients utilizing Mesantoin should be seen at frequent intervals and have complete blood counts once a month during the period of treatment.[22]

*Mephobarbital* (*Mebaral*): This phenobarbital derivative is interchangable with phenobarbital and may be used as a substitute. In equal dosage it is less sedative, but to be as effective as phenobarbital it must be used in double the phenobarbital dosage, at which level its sedative and toxic symptoms are quite similar to those of the latter.

*Metharbital* (*Gemonil*): This drug is used as a phenobarbital substitute. Like Mebaral, it is considered less sedative than phenobarbital, but in effective dosages there is little difference between these drugs. Initial dose is 0.1 Gm. three times a day to a maximal daily dosage of 0.6 Gm. in the adult. It has been stated to be particularly effective in the control of convulsive symptoms due to organic brain damage, but it is doubtful that it has any advantage over other barbiturates in this regard. Its toxicity, while mild, is similar to that of phenobarbital.[23]

*Primidone* (*Mysoline*): This drug is available as a 0.25 Gm. tablet and may be started at this level, increasing by 0.25 Gm. increments at weekly intervals. The average adult effective dose is 0.75 to 1.5 Gm. daily. In children, one-half the adult dose is utilized. Drowsiness, nausea, vomiting, dizziness, and ataxia are toxic manifestations. These symptoms generally subside with regulation of dosage, but on occasion withdrawal is necessary. As a rule, it cannot be given in large amounts with other sedative anticonvulsants, nor in large enough amounts to achieve seizure control without undesirable side effects. It is therefore best used with other drugs usually diphenylhydantoin sodium.[24]

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*Phenacemide (Phenurone):* This drug has been recommended as effective in psychomotor seizures. It is considered one of the more toxic of all the anticonvulsant drugs and is therefore of limited usefulness. In adults the initial dose is 0.5 Gm. three times a day, its therapeutic range being 2-3 Gm. a day. In children half the dosage is used. Serious toxic reactions include personality disturbances with psychotic manifestations, toxic hepatitis, and blood dyscrasias, some of which may be irreversible and fatal. Patients utilizing this drug must be examined frequently and have periodic complete blood counts and liver function tests. It should only be employed if the patient's seizures are psychomotor in type, all other medications have failed, there are no serious pre-existing personality disturbances on history of allergy (especially to drugs), and there is no liver disease. Phenacemide may also produce nausea, vomiting, skin eruptions, and drowsiness.[23]

*Bromides:* Prior to the advent of phenobarbital, bromide was the main compound available for the treatment of epilepsy. While bromides are seldom used in modern practice, and the availablity of other less toxic convulsant meditions makes the need of tolerating the unpleasant side effects of bromides unnecessary, there are occasional patients that may respond to these compounds in whom all other drugs have failed. The initial dose as either the sodium or potassium salt is 1 Gm. twice daily, increasing by 1 Gm. increments at weekly intervals. In children the initial dose is 0.3 Gm. three times daily, with gradual increases by 0.3 Gm. increments until the effective dose is reached. If an adult daily dose of 6 Gm. is not effective, it is unlikely that further increase in dosage will be effective or will be tolerated. During therapy, adequate intake of chlorides must be maintained, to prevent undue replacement of chloride ion in the body fluids by bromide. Serum bromide concentrations are not measured except when it is suspected that the therapeutic range of the drug is being exceeded. The therapeutic concentration in serum varies considerably, from as low as 0.1 Gm. per 100 c.c. in some to ineffective levels of 0.3 Gm. per 100 c.c. in others. Toxic symptoms usually develop with a concentration of 0.15 Gm. per 100 c.c. or more. Bromide toxicity consists of skin rashes, mental dullness, and toxic psychosis.

*Acetazoleamide (Diamox):* This drug is a carbonic anhydrase inhibitor and also has acidifying and dehydrating properties. Its mode of action in epilepsy is unknown. Its effective dosage range is 0.25 to 1.0 Gm. daily. In women who have an increase in seizure frequency during their premenstrual periods, it may be of value as a diuretic agent added during this phase of the menstrual cycle. Large doses produce drowsiness and parathesias. Several instances of blood dyscrasia and renal lesions have occurred.[26]

*Trimethadione (Tridione):* This drug is the compound of primary effectiveness in petit mal epilepsy. Its initial dosage for adolescents and adults is 0.3 Gm. three times a day. Gradual increase is effected until therapeutic levels are reached, usually between 1.5 and 2.7 Gm. daily. In children under 2 years of age 0.15 Gm. two or three times a day is the starting dosage.

Minor toxic reactions seen with Tridione are photophobia, drowsiness, and nausea. Photophobia may disappear with continued therapy or be controlled by the use of dark glasses. Drowsiness and nausea are usually self-limited and

remit with continued therapy. Toxic dermatitis is not uncommon and is usually of the morbilliform or urticarial type. When skin eruption occurs, the drug must be withdrawn immediately but may be restarted at a lower dose increasing slowly by small increments.

The more serious toxic reactions seen with trimethadione are aplastic anemia, agranulocytosis, and nephrosis. Patients utilizing this compound must be examined frequently and should have monthly blood counts. Transient decreases in the percentage of polymorphonuclear leukocytes without an absolute decrease in total leukocytes is not uncommon with trimethadione therapy and does not necessitate withdrawal of the drug. It does require added caution and more frequent blood cell counts. The appearance of signs of renal dysfunction require immediate withdrawal of the drug.[27]

*Paramethadione (Paradione):* This drug, closely related to Tridione, has a similar dosage range and toxicity. It is considered somewhat less toxic than Tridione and is of use in those patients with petit mal seizures who are refractory to therapy or develop toxic reactions with trimethadione. Occasionally, the combination of both drugs gives better results than either one alone. It is necessary to use the same precautionary measures as with trimethadione.[28]

*Phensuximide (Milontin):* Milontin is of value in the treatment of petit mal when Tridione and/or Paradione have been ineffective. Initial dose is 0.5 Gm. three times a day gradually increasing to the therapeutic range of 2 to 3 Gm. per day. Toxic manifestations such as skin rash, somnolence, nausea, vomiting, and vertigo have been noted, as has transient microscopic hematuria.[29]

*Methsuximide (Celontin):* This compound may also be utilized for the treatment of petit mal when drugs of more demonstrated effectiveness have been unsuccessful. It may also have some effectiveness in psychomotor and minor seizures and in abortive seizure phenomena subsequent to reasonably adequate control of major episodes. Adult dosage is 0.3 Gm. three times a day, increasing by 0.3 Gm. increments at weekly intervals. Somnolence and ataxic gait are not uncommon side reactions. Skin rash, hepatic damage, albuminuria, and personality changes have also been noted.[30,31]

*Ethotoin (Peganone):* This is the newest commercially available anticonvulsant of the hydantoin series. Its indications are as with Dilantin. Initial adult dosage is 0.5 Gm. a day. Effective range has been between 3.0-4.0 Gm. daily. Toxic manifestations of somnolence, rash, ataxia, and gastrointestinal upset have been noted but have been mild. Peganone is far less effective than Dilantin as an anticonvulsant but has been of value in some refractory cases, usually in combination with other compounds.[32]

*Amphetamines (Benzedrine, Dexedrine):* The amphetamines are of value in counteracting the somnolence due to other drugs and, in conjunction with Tridione and/or Paradione, in the reduction of petit mal attacks in children. Dosage varies from 2.5 to 20 mg. a day in tablet form or in sustained release spansule preparations. Barbiturate-induced hyperactivity in children may paradoxically be improved with the addition of small amounts of the amphetamines.[33]

*Ketogenic diet:* Starvation and dehydration with resultant acidosis has long been known to decrease the frequency of seizures. Livingston feels it is the best therapy for minor motor seizures in children. Production of an acidotic state

by a diet containing an excess of fats over carbohydrates can be accomplished. Its maintenance, however, is extremely difficult, particularly in children, the very group whose seizures are most suitable for this type of therapy. It is rarely used today.[34]

### FEBRILE CONVULSIONS

A commonly occurring special therapeutic problem is that of the child below the age of 3 years with nonspecific infection, who with fever has seizure phenomena. These convulsive episodes are grand mal in type but may be associated with focal elements in terms of onset, movement, or postictal Todd's paralysis. Such manifestations in children of this age are not necessarily correlated with structural defect and may represent an inequality of cortical discharge without any significance. When the child is seen after the seizure episode and has returned to perfect normalcy and an afebrile state, the problem is simplified. The earlier in the course one sees the patient the more difficult may be the immediate evaluation, for the occurrence of a seizure in the presence of a febrile illness for which there is no obvious cause should in young children lead to a suspicion of meningitis. A convulsion may be the first manifestation of meningitis without meningeal signs. In younger infants with adequately treated meningitis, the appearance of seizures suggests the possibility of a subdural effusion. General measures to reduce fever in terms of aspirin, sponging, and, if possible, specific therapy for the infection are of prime importance. Management beyond the infectious episode is of equal importance. Lennox has shown that febrile convulsions may later become recurrent idiopathic seizures. This is particularly true if initial seizure phenomena occur before the age of 1 or after the age of 3, if the electroencephalogram is abnormal and if the seizure episode has been particularly severe or prolonged. It is unusual for a child to have only one febrile convulsive episode. Subsequent episodes may be severe and damaging. In order to avoid this the patient may be maintained on anticonvulsant medication, usually phenobarbital, until 3 to 5 years of age. The majority of physicians do not initiate anticonvulsant therapy after only one febrile seizure episode, but prefer to wait until a second or a third. Others feel the incidence of recurrence is so high and the subsequent severity of seizure so unpredictable that phenobarbital should be initiated after the first episode.[35,36]

### STATUS EPILEPTICUS

Status epilepticus consists of seizures occurring with such frequency that the postictal phase of one episode merges with the seizure discharge of the next, the patient never fully regaining awareness. It may last hours to days.[37]

The over-all goal in the therapy of status is to control the episode expeditiously, continue that control, and at the same time maintain the patient in as normal a physiologic state as possible. Grand mal status is always a potentially lethal and emergency situation. General measures in terms of maintenance of an adequate airway, oxygenation, blood pressure, hydration, and preventing self-damage must be taken. The common errors repeatedly observed in specific

therapy are often a function of the antistatus drugs employed in terms of their dosage and manner of administration. Drug therapy in this condition must be parenteral. Since one desires rapid action and dependable absorption, the intravenous route is indicated. The short and intermediate acting barbiturates, with the exception of amobarbital, are less consistently effective in stopping seizures than is phenobarbital. The former are often associated with a transient but definite hypotensive effect which may in some older patients be dangerous. Regardless of the drug chosen, the full calculated anticonvulsive dose must be given initially. Utilization of drugs in small aliquots, particularly the barbiturates, may result in the paradoxical situation of an individual depressed by barbiturates but who is still in status. Phenobarbital or amobarbital sodium may be given in 0.4 to 0.8 Gm. doses intravenously in adults and 0.2 to 0.4 Gm. in children. A drug that is equally effective is paraldehyde. This, too, must be used intravenously, 3 to 6 c.c. in adults and 2 to 4 c.c. in children.

Parenteral Dilantin is now available and theoretically should be the drug of choice in that it is considered a more specific anticonvulsant and does not depress respirations. The solution is prepared in a 50 mg. per cubic centimeter solution and administered intravenously at the rate of 1 c.c. per minute for a total initial adult dosage of 250 mg. A repeat dosage of 100 to 250 mg. may be given in 30 minutes if cessation of seizures has not occurred. Dosage for children is proportionate to weight considering an average 150-pound adult.[38,39]

As soon as status has been terminated, a plan of anticonvulsant control to prevent recurrence of the syndrome and isolated seizures is undertaken. Intramuscular phenobarbital covering the patient over a 48-hour period or until adequate oral medication can be effected and Dilantin or other slower acting drugs have had time to reach effective levels is essential.

Episodes of petit mal status are comparatively rare, are often difficult to recognize, and may masquerade as an acute psychiatric syndrome. Treatment consists of air rebreathing to increase $CO_2$ concentration, oral medication with Tridione or phenobarbital during cooperative periods, or, if these fail, intravenous phenobarbital as in grand mal status.[40]

*Surgical Therapy.*—Excluding patients with seizures secondary to intracranial mass lesions, there is only a small group with static defects due to focal pathology that present indications for surgery.

Criteria for surgery are: (1) the convulsive episodes and related phenomena should be of such type and frequency that the individual is socioeconomically severely incapacitated, (2) an adequate trial of drug therapy must have been unsuccessful, and (3) consistent clinical and electrical focality must exist.

Temporal lobe surgery for intractable psychomotor seizures has limited application, but in selected patients may be of value in management.[41]

Hemispherectomy in cases of infantile hemiplegia with uncontrollable seizures and personality disturbance has resulted in improved behavior and seizure control, without increasing the neurologic deficit, and often decreases the presenting hemiparetic spasticity.[42]

*Reduction and Elimination of Therapy.*—Most patients after varying seizure-free periods will inquire as to the reduction or elimination of their medication.

The handling of this problem must be highly individualized and take cognizance of what a seizure may mean to an individual, his career, and his family. Spontaneous or therapy-induced remissions may occur even in those with structural brain defects, such as the post-traumatic group.[43] After 2 to 3 years of freedom from seizures, gradual drug reduction may be attempted over a year or more. The results of drug elimination or reduction, except in petit mal episodes, has been disappointing. The patient has at least a 50 per cent chance of seizure recurrence, and the likelihood of recurrence bears no relationship to the duration of pre-existing freedom from seizures while on medication.[21] This degree of calculated risk must be realized before subjecting a patient to a drug reduction program.

*Effectiveness of Therapy.*—The ideal anticonvulsant in terms of absolute effectiveness regardless of seizure type, and lack of all toxicity is not available.

Advances in drug therapy continue, and with future compounds and further pathophysiologic knowledge the inadequacies of current therapy will be diminished. At present, however, maximum proper utilization of the most effective drugs, for the seizure type presenting, is required if the 75 to 80 per cent degree of seizure control possible is to be obtained.

Yahr indicates that the possibilities for adequate seizure control in petit mal are greatest with Tridione and/or Paradione; all other drugs have contributed only 5 per cent additional control. Should Dilantin alone or in combination be ineffective in the control of major seizures, all other drugs result in only 10 per cent additional control.[44]

These highly effective anticonvulsant compounds must be maintained at tolerance for a sufficient period to judge their effectiveness before other drugs are utilized.

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## SUMMARY

1. Current concepts of the pathophysiology of the convulsive disorders, and their clinical manifestations are presented.

2. The fundamentals of medical therapy and commercially available anticonvulsants are discussed.

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# MULTIPLE SCLEROSIS

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## INTRODUCTION

MULTIPLE sclerosis, a disease of the central nervous system affecting chiefly the white matter of the brain and spinal cord and singularly sparing the peripheral nervous system, remains an unsolved problem of medicine. Well established are only the descriptive facts of morbid anatomy, the long familiar clinical course, much of the pathologic neurophysiology, and more recently its epidemiology. As yet without solution are the individual problems of etiology, pathogenesis, early clinical diagnosis, laboratory diagnosis, prognosis, and treatment. The sociologic problems created by the disease have only recently come into focus.[1,2]

The disorder has been classified under the "demyelinating diseases," though there is yet no satisfactory definition of the latter group of conditions, and the relationship of multiple sclerosis to other members of this group remains uncertain. The outstanding characteristics of the condition are (1) discreteness and multiplicity of lesions with consequent widespread symptoms and clinical signs of neural dysfunction; (2) the reversibility of the lesions in the earlier stages of the disease in many patients, permitting complete or partial recovery from symptoms; (3) the development of gliosis, scarring, and permanent damage in the areas repeatedly affected, leading to a chronic progressive downhill course and death in the majority of patients. Thus, the disorder, generally episodic and remittent at first, may ultimately lead to chronic invalidism and severe disablement. Since the cause of multiple sclerosis is unknown, it is unsettled whether the illness is a specific disease entity or a syndrome of multiple causation.

## EPIDEMIOLOGY AND STATISTICS

The age of onset has been shown in many studies to fall predominantly in young adulthood, approximately two-thirds of patients having their first symptoms between the ages of 20 and 40. The incidence is less in the second and fifth decades, but even before the age of 10 and after the age of 50 a definite though very small incidence of onset has been shown. Though earlier studies indicated an approximately equal sex incidence, a summary of more recent reports[3] indicates the probability of a somewhat higher incidence in female patients, ranging from 54 to 64 per cent of cases.

The occurrence of the disease in the population has been the subject of numerous surveys in recent years which have been well summarized.[2,3] Such surveys have shown multiple sclerosis to be one of the most frequently occurring of all neurologic disorders. The incidence and prevalence have been shown to vary in different countries and in different geographic areas of the same country. Studies have indicated that the incidence is higher in the northern hemisphere and that in the northern hemisphere the incidence is progressively greater the more distant the latitude from the equator. This latter association is derived chiefly from statistics in the northern hemisphere since statistics published in countries in the southern hemisphere are not detailed enough to demonstrate a definite relationship between mortality and latitude.

Prevalence rates in the northern European countries and Great Britain are high by comparison with the rest of the world and comparable to those found in the northern United States and Canada. In North America the incidence, prevalence, and mortality rates are much higher in the northern states and Canada than in the southern states. Thus, in the northern parts of the United States and in Canada prevalence rates range from 40 to 60 per 100,000 population, whereas in certain southern cities a prevalence rate of 11 to 13 per 100,000 has been determined. This may be contrasted with the extremely high prevalence rate found in one northern county of Scotland, namely, 113 to 129 per 100,000.[4] Other localized areas of increased concentration of patients have been reported both in Great Britain[3] and this country. The attempt to correlate such geographic incidence with possible etiologic factors is discussed below.

Estimates of the total number of patients ill with multiple sclerosis in the United States have ranged from 70,000 to 250,000.[2] The latter figure is based on the probable existence of numerous cases undiagnosed and unreported and of patients with only minor incapacitation for many years who do not seek medical attention.

## PATHOLOGY

The morbid anatomy of disseminated sclerosis has been known for over a century. The gross appearance of the brain and spinal cord varies considerably with the stage of the disease. Well-circumscribed islands of change in the white matter are found, which are apt to be somewhat pinkish and soft in the fresh or early lesions but pearly gray, somewhat translucent, and more firm in the later stages. The lesions may overlap or actually invade gray matter (e.g., cerebral or cerebellar cortex, the brain-stem nuclear tissue, or spinal cord horns), but this is not characteristic and far less common than white matter involvement.

Microscopically the features of the fresh lesion are hyperemia, fragmentation of myelin sheaths, more or less preservation of axons, perivascular infiltration, and proliferation of glial macrophages and glitter cells, usually fat laden with the products of myelin disintegration. Some authors consider the inflammatory cells a secondary response to the products of disintegration but not an integral part of the primary lesion.[5] A periventricular localization in the cerebrum is common and perivenous distribution is reported by most pathologists.[6-8] Throm-

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bosed venules[9] or dilated veins showing stasis of blood or sludge formation[10] in the centers of plaques have been described. These have been considered by some as likely causative factors but thought by others to be secondary to the primary lesions[11] and not to play a role in their genesis.[12] A recent study minimized the perivenous localization of lesions and denied altogether the existence of vascular occlusion or thrombosis in relation to plaque formation.[13] The resemblance of the histologic picture to the lesions in allergic encephalomyelitis experimentally produced in animals[14] as well as other histologic features[8] have emphasized the possible hyperergic causation of the lesions.

The older, grayish plaques are found on microscopic examination to show gliosis where a former acute process has destroyed axons as well as myelin. Such damage is followed by the formation of a central nervous system scar or meshwork of glial fibers replacing the damaged parenchyma. In pathways where scars have destroyed nerve fibers there is distal Wallerian degeneration. When a large number of such lesions has occurred in the cerebrum, there may be some degree of shrinkage of the parenchyma and dilatation of the ventricles.

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### PATHOLOGIC NEUROPHYSIOLOGY AND CLINICAL SYMPTOMATOLOGY

The abnormalities of nervous function are the result of temporary or permanent loss of conductivity along nerve fiber pathways of the long ascending and descending tracts of the spinal cord, the shorter intersegmental fiber bundles of the brain stem, and the large masses of subcortical fiber tracts of the cerebrum and cerebellum. The neurologic dysfunction thus consists of motor and sensory deficits and disturbances in personality and mentation. Since asymmetric arrangement of lesions predominates, at least during the earlier remittent stages of the disease, the motor and sensory impairment is also apt to be initially asymmetric. In the later stages, the wide scattering of demyelinized and scarred areas leads to a gradual equalization of the disturbed functions on the two sides of the body.

Involvement of the pyramidal tracts (corticobulbar or corticospinal) at any point from the subcortical white matter through the brain stem to the spinal cord gives rise to weakness with features of spasticity, hyperreflexia and clonus, loss of superficial abdominal reflexes, extensor toe responses, and eventually atrophy and contracture of muscles, especially hamstrings and calves. Similar disturbances of the motor functions of the head referred to as pseudobulbar palsy resulting from involvement of the corticobulbar portion of the pyramidal pathway may lead to spastic dysarthria, dysphagia, impaired strength of mastication, and overactive jaw stretch reflex, weakness of the facial muscles, especially the lower, on voluntary effort with at the same time hypermobility of the facial muscles on emotional implementation (lability of emotional expression), and facial muscle hyperreflexia, including a snout reflex and palmomental reflexes.

Interference with control of bladder and bowel function is common. Frequency, urgency, and slight incontinence are the earliest symptoms of bladder dysfunction, with retention and severe incontinence developing later. The loss of control undoubtedly is related to involvement of the efferent suprasegmental

pathways in or adjacent to the pyramidal tracts of the cord and to lesions in the posterior funiculi. Frontal lobe lesions may also contribute to incontinence. The pathophysiology of rectal dysfunction is the same as that of the bladder.

The outstanding symptom of constipation is analogous to retention in the bladder. It is more common than rectal incontinence only because the more solid content of the rectum leads to greater difficulty of evacuation. If the feces are liquid, incontinence of the rectum occurs as readily as that of the bladder.

Involvement of the posterior funiculi in the spinal cord or their upward continuation in the brain stem via the secondary relay (medial lemnisci) leads to impairment of proprioceptive sensations, especially position and vibration sense, and of discriminative sensibility of the hands. An impairment of recognition of common objects through grasping them ("dysstereognosis") combined with incoordination of the finer movements leads to a characteristic and severe disability referred to originally by Oppenheim[15] as "the useless hand." A characteristic, almost pathognomonic symptom of multiple sclerosis, resulting from a plaque involving the posterior columns of the cervical cord, is the occurrence of tingling or electric-like paresthesiae extending into the limbs or trunk on flexion of the neck, Lhermitte's sign.[16] A prevalence of involvement of the posterior portion of the spinal cord in the cervical region and clinical sensory manifestations of spread of such lesions by "focal diffusion" have been shown in a collected series of cases.[3,17]

The spinothalamic pathways of the cord, conducting pain and temperature, are much less frequently involved, with consequent lesser impairment in these sensory modalities. The descending root of the fifth cranial nerve is, however, occasionally involved with either a sensory defect on one side of the face or an irritative manifestation of pain resembling trigeminal neuralgia. Pain is in general infrequent in multiple sclerosis, especially in locations other than the face. Nevertheless, it may infrequently occur elsewhere, as for example, in a limb or the trunk when an inflammatory or gliotic plaque happens to be so located as to irritate the incoming pain fibers of a sensory nerve root. When the sensory fiber involvement is in the subcortical white matter of the cerebrum, that is, in the neurones from thalamus to the parietal cortex in the posterior limb of the internal capsule, the defects are in the realm of discriminative sensory functions rather than in isolated individual modalities.

Involvement of the short fiber pathways of the brain stem is most strikingly manifested by the disruption of function of the posterior longitudinal bundle (medial longitudinal fasciculus) providing intersegmental integration of eye movements, with dissociation of the conjugate gaze mechanism and the development of nystagmus, which may be vertical (on upward gaze) as well as horizontal (on lateral gaze). Involvement of the interconnections within the vestibular complex may lead to vertigo. Lesions of the cochlear-trapezoid interconnections for hearing and their upward extension in the suprasegmental pathway for hearing (lateral lemnisci) on rare occasions may produce hearing impairment or severe tinnitus, practically always bilateral. Pathologic somnolence has on infrequent occasions been noted in multiple sclerosis, presumably related to involve-

ment of the fibers of the reticular substance of the brain stem or of the hypothalamus. Because of the close relationship of fiber pathways in the brain stem to cranial nerve nuclei and a strong predilection for lesions in this region of the central nervous system, it is not surprising that occasionally gray matter becomes involved. Consequently, one may occasionally see ocular palsies or facial weakness that is more characteristic of segmental gray matter (i.e., lower motor neurone) dysfunction than of white matter (intersegmental or suprasegmental) dysfunction.

Involvement of the cerebellar subcortical white matter or of the cerebellar connections leads to ataxia of station or gait, intention tremor, and to decomposition and incoordination of movement of the limbs. The dyssynergic alteration of speech produced by cerebellar involvement has been referred to as scanning speech.

Disturbances from lesions in the cerebral white matter have already been referred to in connection with lesions of the motor and sensory components of the internal capsule. Lesions still further posterior in the internal capsule involving the optic radiations (temporal or occipital) may produce homonymous field defects.[18] Similar homonymous visual field defects may occur when lesions develop in the optic tracts or chiasm.[19] The common lesion anterior to the optic chiasm in one or the other optic "nerves," referred to as retrobulbar neuritis, frequently produces unilateral impairment of visual acuity with associated central or paracentral scotomas, and at times even total blindness (usually unilateral). Though severe visual loss is virtually always temporary, residual impairment of vision and the later appearance of pallor of the optic disk are common aftermaths of an attack. Repeated attacks at these sites may lead to permanent near-blindness, but this is seldom found save in terminal states in patients severely involved otherwise. That optic neuritis, better termed optic or retrobulbar neuropathy, is caused in the majority of instances by multiple sclerosis, even when unassociated with other neurologic manifestations and even when not followed for years by recurrence, seems well documented.[20-22]

Other cerebral lesions probably involving chiefly the frontal connections with the thalamus, hypothalamus, and brain stem undoubtedly give rise to the rather characteristic personality changes and, in later stages, to mental impairment. Even the pre-illness personality functions in multiple sclerosis have, however, been shown by psychiatric studies to reveal emotional abnormalities, notably immaturity, long before signs of organic disease.[23] Hysterical symptoms preceding or associated with the disease are not infrequently encountered.[24-26] It is possible that these premorbid traits may in fact be related to an extremely early phase of the disease process and that subtle personality changes in the absence of other neurologic manifestations are the result of minute frontal lesions.

Euphoria, a benign, cheerful outlook with apparent disregard of physical disability, and with optimism, friendliness, and good spirits, is a striking feature in probably the minority of patients and may be an early sign quite helpful in differential diagnosis. It is the experience of most clinicians, however, that irritability, querulousness, lack of stamina, emotional instability, and depressive mood tendencies are as characteristic of the earlier stages as is euphoria.[27] These

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features may give way to euphoria later or persist throughout the duration of the disease.

Gross impairment of intellectual functions is a late feature of the disease in a proportion of patients. The manifestations are: decline in interest, concentration and efficiency, loss of memory, and poor judgment, leading in severe cases to a terminal vegetative state. Clinically obvious mental impairment, however, may not occur, since cerebral involvement may be slight. Psychologic investigations of groups of patients including controlled quantitative study of intellectual and affective functions have provided scientific support for these clinical impressions.[28,29] In acute fulminating episodes, of course, massive demyelination of the brain may cause transient stupor, or even coma leading to death.

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## ETIOLOGY AND PATHOGENESIS

There has been no paucity of hypotheses as to the etiology of multiple sclerosis, but final proof of causation has not been established. Theories are quite diverse and embrace most of the major categories of causation of human disease save for neoplasm. Among the many proposed etiologic factors have been unknown factors, possibly hereditary, leading to chemical, metabolic, or enzymatic disturbances, lesion production through exogenous nutritional factors, specific infection, vascular causes, and allergic reactions of nervous tissue due to hypersensitivity. A variety of precipitating, associated, or contributing factors, some operating possibly as links in the chain of pathogenetic events, has been cited.

*Hereditary Factors.*—Most studies of this problem over the past half century have recognized the occurrence of a definite familial incidence but have not emphasized its magnitude or importance. Recent studies have shown this incidence to be higher than expected by chance, averaging about 6.5 per cent.[30-34] Though one study stated that genetic factors were not operative,[35] constitutional vulnerability due to hereditary predisposition is now considered as a strong etiologic factor in the opinion of most authors. The specific mechanism through which such a familial tendency operates is as yet unknown.

*Chemical, Metabolic, or Enzymatic Disturbances.*—No specific so-called inborn error of metabolism in the form of a regularly present abnormal product of incomplete metabolism in the body fluids or excretions, or specific enzymatic failure has been discovered. Investigation of the chemical constituents of blood and spinal fluid, however, including protein fractions, amino acids, phospholipids, lipoproteins, and the investigation of glucose metabolism and phosphorus metabolism have all revealed abnormalities in the group as a whole. To what extent these changes represent primary or secondary factors in causation, reflect concomitant changes or associated events, or are the effects of the disease, remains unclear. Some of the changes have been shown not to be specific for multiple sclerosis alone but to occur in other organic nervous system diseases as well.

*Nutritional.*—Vitamin deficiency is no longer considered a tenable cause. A former dietary survey indicating deficient fat intake and more recent epidemiologic[36,37] and experimental studies[38,39] in human beings and dogs invoking the pathogenetic role of a high fat diet in the genesis of lesions have not been con-

firmed. The latter studies postulated a basic defect in the suspension stability of the blood of patients with multiple sclerosis which might be upset by the hyperlipemia following heavy meals, leading to vascular lesions in the nervous system.

*Infection.*—Infection with an unidentified virus or specific organism is still considered a possible cause. There is little substantial evidence to support these notions, most studies having reached conclusions on presumptive grounds. Multiple sclerosis has never been produced by the inoculation of an infectious agent in animals. Man-to-man transmission through contagious vectors seems highly unlikely.[40] Infection by a virus has been neither proved nor disproved to date.[41] The concept of virus infection operating as a primary damaging agent to central nervous system tissue followed by secondary allergic reaction has been proposed but still remains an hypothesis (*vide infra*). Theories in regard to the possible etiologic role of streptococcic and Brucella infection have emerged and been refuted during the past decade (*vide infra*).

For decades some investigators have raised the possibility that multiple sclerosis is a form of metatuberculosis. Positive complement-fixation tests for tuberculosis in a majority of multiple sclerosis patients have been cited.[42,43] Mycobacteria were recently alleged to have been isolated from the cerebrospinal fluid.[44] Reports of therapeutic benefit from the treatment of multiple sclerosis with isonicotinic acid hydrazide (Isoniazid) appeared to lend weight to this possibility, but subsequent investigations have failed to confirm the therapeutic efficacy of this antituberculosis compound (*vide infra*).

Intrathecal injection of tuberculin in normal and multiple sclerosis patients with negative Mantoux tests has been shown to produce no reaction in the meninges. When the Mantoux test is positive, the intrathecal injection of tuberculin in otherwise normal controls produces a severe reaction closely correlated with the intensity of the Mantoux reaction and characterized by a polymorphonuclear and later lymphocytic pleocytosis and a variable rise in protein in the cerebrospinal fluid, thus indicating a true antigen-antibody reaction. In multiple sclerosis patients with positive Mantoux tests, however, polymorphonuclear pleocytosis is absent following intrathecal tuberculin injection but a far greater rise in protein content occurs. This distortion of the reaction has been interpreted to mean that normal immunologic processes in multiple sclerosis are disordered.[45]

The theory of spirochetal origin[46] long held but never generally accepted, has recently received fresh impetus from the report of darkfield demonstration[47] and successful culture[48] of spirochetes in the spinal fluids of multiple sclerosis patients. Other investigators have not duplicated these results, and the alleged demonstration and cultivation of spirochetes in multiple sclerosis remains unconfirmed.

*Vascular.*—Recurrent, scattered, multiple areas of vasoconstriction have been postulated on the basis of such changes in retinal arteries.[49] Alleviation of symptoms in multiple sclerosis patients as well as the disappearance of signs have been alleged to result from various techniques of vasodilatation (*vide infra*). Much of this work remains unconfirmed by other investigators. Pathologically, the perivenous distribution of multiple sclerosis lesions in the nervous system

has been unequivocally established. However, the alleged occurrence of venous thrombosis in the center of lesions, of "vasoparalysis" with stasis of blood (sludge) in the region of lesions, abnormalities of vein walls, or disorder of the blood clotting mechanism all have remained largely unsupported by the findings of other investigators. Where such changes have occured it could not be shown whether the change was a primary cause of the lesion or merely associated with or secondary to the primary lesion. Indirect support for this hypothesis is the alleged therapeutic benefit from prolonged anticoagulant therapy (*vide infra*).

*Allergy.*—The work on acute allergic encephalomyelitis has suggested that the inciting factors or conditions leading to the development of multiple sclerosis might possibly be related to abnormal immunologic mechanisms.[50,51] Histopathologically there is presumptive evidence that the lesions of multiple sclerosis represent areas of hyperergic tissue reaction in the white matter of the central nervous system.[8,14] A sequence of events that has been proposed in the pathogenesis of multiple sclerosis is the development of a primary lesion in the white matter by a cause as yet unknown (possibly virus infection) leading to the liberation of products of disintegration which act as autoantigens causing the development of antibodies which subsequently react with normal central nervous system tissue to produce scattered hyperergic inflammatory lesions.[52,53]

Clinically, the evidence to support the allergic theory of multiple sclerosis is unsatisfactory. The incidence of atopy is the same as in the general population.[54,55] Occasional instances have been reported of the concomitant occurrence of allergic manifestations in the skin or respiratory tract and fresh symptoms or signs of multiple sclerosis,[3] but there is no proof of precipitation or exacerbation of the disease due to specific food ingestion or other contact. Though the incidence of positive reactions to skin and conjunctival sensitivity tests has been reported higher than in the general population,[55] such tests are of little value in proving a nonreaginic type of allergy.[56,57] All the evidence bearing on this problem cannot be included in this review. For a more comprehensive discussion the reader is referred elsewhere.[3]

*Factors Related to Geographic Incidence.*—The suggestions that multiple sclerosis might be due to high fat content of the diet, to deficiency of copper in the soil, to lead intoxication, streptococcus infection, or to brucellosis are all theories derived from alleged geographic associations. As already mentioned in the discussion of nutritional factors, an epidemiologic survey in northern Europe covering the period during and after the war suggested that incidence of multiple sclerosis varied directly with the consumption of fat.[36,37] The development in an area of Britain of a demyelinating disease in lambs called "sway-back" due to deficiency in the soil of the trace elements copper and cobalt, with a coincidental occurrence of an outbreak of multiple sclerosis in humans in the same area led to a study of these factors without conclusive results.[58,59] In another area of England, where the soil content of lead was high, there was a concentration of cases of multiple sclerosis and higher than average concentrations of lead were found in the teeth,[60] but lead intoxication remains an unlikely cause of multiple sclerosis.

The similarity of the geographic distribution of multiple sclerosis and rheumatic fever has suggested a relationship to streptococcus infections, but antistreptolysin titers in a large group of patients with multiple sclerosis were not abnormal. Brucellosis was proposed as a cause because of similar geographic incidence and the frequency of positive serologic and skin tests for brucellosis in patients with multiple sclerosis, but these conclusions have been contradicted.

Epidemiologic surveys have raised the question as to why multiple sclerosis apparently is a cold climate disease. Though climate in itself, specifically cold weather, has not been definitely shown to be a factor in the pathogenesis, the strikingly high incidence of the disease in northern latitudes undoubtedly indicates some causal relationship.

*Psychogenic Factors.*—Personality factors are of great interest and may be important in pathogenesis. Whether they play a specific etiologic role is uncertain, though the alleged finding of common premorbid personality traits has led to the proposal that certain emotional factors contribute to causation and that life stresses with attendant pernicious emotional reactions may lead to exacerbations.[23,61,62]

*Miscellaneous Factors.*—Attention should be called to a variety of possible noxious influences that have seemed to contribute to the precipitation of first or recurrent attacks of the disease. Among these, in addition to emotional stress, are fatigue and overwork, chilling, acute infections (especially upper respiratory), operations, anesthesia, pregnancy, and injuries. Statistical evaluation of the incidence of association of some of these factors (infection, operation, pregnancy, injury) has lent some support to but has not proved the validity of the claim that they are important as precipitating factors.[3,63-66] The mere number of such different factors suggests their nonspecificity and the likelihood that a general lowering of health and resistance accompanying these states may be the common factor.

## CLINICAL COURSE

The neurologic symptoms and signs in patients with multiple sclerosis have been referred to in the discussion correlating the structural damage with the clinical manifestations. Such a discussion does not convey a picture of the natural history of the disorder as it affects different patients. Because of the variation in severity, size, number, location, and frequency of occurrence of the lesions, it is obvious that no two patients will present the same cross-sectional pattern of neurologic dysfunction nor the same longitudinal course of illness. Numerous statistical analyses and summaries have been made of the frequency and temporal relationships of various symptoms and signs, the natural history, course, and duration of the disease and of prognostic factors.[2,3,24,30,63,67-71] Though some of these statistical studies have shown that some particular features of the course of the disease can be utilized in a predictive or prognostic way, the exact course of the disease in any given individual cannot be predicted with accuracy.

The duration of the disease may vary from a few months to many years. An acute, fulminating course can lead to death within a period of 6 to 12 weeks. It is in such cases that the differentiation from acute disseminated encephalo-

myelitis is difficult. In some patients there is a fairly rapid downhill course terminating in death in 5 to 10 years. Such patients usually have a number of recurrent, rather severe episodes with intervals of relative recovery during the first few years, but are left with increasingly severe residuals following successive exacerbations and succumb within a year or two after becoming bedridden. A third, more chronic pattern is characterized by relatively minor attacks of brief duration (days or weeks), separated by asymptomatic intervals of years, and followed eventually by slowly and insidiously progressing disability. Such a slow steady course with minor fluctuations eventually leads to some degree of chronic disability after 10 to 20 years but may not materially shorten the life span. Rarely a few widely spaced attacks may occur early in life, never to be followed by subsequent recurrence or by progressive disability, the disease presumably remaining quiescent throughout the balance of a normal life span. Finally, there is a type characterized by a gradually progressive motor disability from the outset and a slow, steady downhill course, with only slight fluctuations in symptomatology, insufficient to be termed remissions or relapses. When the disease has its onset after the age of 40, it is apt to run this type of course and in general has a poorer prognosis than the remittent type beginning before the age of 25.

Thus the disease may last a very short time and be responsible for death in a few weeks to several years; or it may last indefinitely and not shorten the life span at all. Cases are on record in which the disease has been present for 40 to 60 years.[13,26] Attempts to arrive at an average figure for the duration of the disease have little value when the range of duration is so wide. Nevertheless, the average duration of the disease has been computed in various ways from several sets of statistics leading to figures of from 9 to 27 years.[3] Numerous studies investigating the attrition rate in the course of the disease, though providing a more realistic view of its natural history, will not be summarized here inasmuch as differences of material, duration of follow-up, and frame of reference have led to different results. One analysis showed that in a group of patients ambulatory when first seen, and followed for approximately 15 years, slightly over two-fifths were still ambulatory, slightly over one-quarter were partly or totally helpless, and well under one-third were dead at the end of this time.[72] Another report,[70] showing that the prognosis both as to disability and life is less serious than formerly thought, stated that 60 per cent of the patients were without disability 5 years after onset, 38 per cent after 10 years, and 13 per cent after 15 years. The results of various studies of the course and prognosis in multiple sclerosis have been presented in greater detail and are well summarized elsewhere.[3]

## DIAGNOSIS

*Laboratory Findings.*—There is no laboratory test specific for multiple sclerosis. The alleged demonstration of a spirochete by centrifugation and dark-field examination of the cerebrospinal fluid[47] and the reported isolation by spinal fluid culture of a spirochete allegedly specific for multiple sclerosis[48] have not been

confirmed to date by other investigators. Positive complement fixation tests utilizing antigens derived from human multiple sclerosis tissues have been reported but not come into general use.[73,74] Numerous biochemical, hematologic, and physiologic abnormalities that occur in patients with multiple sclerosis are either too nonspecific for use as diagnostic procedures or involve techniques of measurement suitable only for the research laboratory. Among such are the altered distribution of protein fractions in the blood and cerebrospinal fluid with reduction in the serum albumin-globulin ratio and a significant increase in the concentration of gamma globulin,[75-81] and changes in the glycoprotein patterns of the cerebrospinal fluid.[82] Defects in the Krebs cycle of glucose metabolism,[83-85] alterations in protein metabolism, increase in serum cholinesterase and decrease in serum adenosine triphosphatase,[84] and impairment of glutamic acid metabolism in the brain[86] are aspects of pathologic physiology that have come to light in the systematic investigation of metabolic functions in multiple sclerosis. These alterations have not as yet served to provide help in diagnosis or understanding of pathogenesis.

The blood count, sedimentation rate, and urinalysis (save in response to the common late complication of secondary infection), routine blood chemistry values, and the bleeding and coagulation times are all within normal range. Lowered capillary resistance,[87] increased blood platelet adhesiveness,[88] occurrence of thrombocyte-agglutinating substance in the cerebrospinal fluid,[89] increased clot retraction time,[90] fluctuation in the number of circulating platelets with fall during active phases followed by rise during improvement,[91] sludge formation in blood vessels,[92] and variations in plasma fibrinogen during the course of multiple sclerosis suggesting an increase during exacerbation[93] have been reported.

The cerebrospinal fluid is often entirely normal in multiple sclerosis. Though its content may be abnormal at any stage of the disease, only infrequently does a patient with multiple sclerosis exhibit changes in all of the tests that are usually done, namely, cell count, qualitative protein test (Pandy), total protein content, and colloidal gold reaction. Slight to moderate change in one or more of these elements has, however, been reported in 78 per cent of one series[94] and in 57 per cent of another.[3] The usual order of rise in mononuclear cells, if present, is to 5 to 10 per cubic millimeter, rarely as high as 50 to 100 cells per cubic millimeter. The usual order of elevation of protein content, if it occurs, is to 50 to 60 mg. per hundred milliliters, rarely as high as 75 to 100 mg. per cent. The incidence of first zone colloidal gold curve elevation is probably less than generally thought. Various studies have reported colloidal gold changes, from 9 to 80 per cent of the cerebrospinal fluids of multiple sclerosis patients, depending on the technique and interpretation. It is likely that by the routine hospital laboratory method about one-third to one-half of spinal fluids in patients with multiple sclerosis will show abnormal colloidal gold precipitation, less than half of these in the first zone. A newer technique of quantitatively standardized gold sol reactions, differentiating curves into seven types, has revealed a 90 per cent incidence of a specific pattern of curve, called "Type D" in the fluids of patients with multiple sclerosis.[95,96]

The electroencephalogram is abnormal in roughly half of the patients with multiple sclerosis, but the patterns of irregular rhythm are not diagnostic of the disease. Pneumoencephalograms generally are normal, but in later stages may show slight asymmetric dilatation of the ventricles and increase in the amount of subarachnoid air over the hemispheres, bespeaking moderate cerebral atrophy.[97] One case of multiple sclerosis has been reported with a transient electroencephalographic focus and ventricular displacement on pneumoencephalography simulating brain tumor.[98] Both abnormalities disappeared within 3 months after subsidence of acute symptoms. Of interest in this patient was a slight rise in pressure to 210 mm. of cerebrospinal fluid and moderate protein elevation to 68 mg. per cent.

As a laboratory procedure useful in supporting the diagnosis of multiple sclerosis, visual field testing often yields results in the form of central or paracentral scotomas. A new method of measurement of visual function in which the threshold of visual flicker-fusion is determined in various fields has been applied to patients with multiple sclerosis.[29,99] This has shown an impairment in flicker-fusion discrimination in the majority of patients with multiple sclerosis even when the visual defects are not revealed by standard methods of examination. The rare occurrence, previously referred to, of homonymous hemianopia[18,19] is another finding not inconsistent with the diagnosis of multiple sclerosis, though central or paracentral scotomas are far more common.

*Clinical Diagnosis.*—Diagnosis is made most dependably on the basis of history and neurologic findings. On such clinical grounds it is closely related to the euphemism that multiple sclerosis is a disease "scattered in time and space." Two important features weigh heavily in diagnosis: (1) evidence of fluctuations in the course of the disease, either with well-defined remissions and exacerbations or with lesser fluctuations against a background of more or less steady progression; and (2) the elicitation of symptoms and the demonstration of signs indicating scattered lesions in the white matter of the central nervous system.[100]

*Differential Diagnosis.*—Because of the variety of symptoms and signs, multiple sclerosis may resemble any of a number of other diseases of the nervous system. Of considerable importance is the differentiation of multiple sclerosis from surgically remediable conditions such as spinal cord compression. This is essential when symptoms or signs are limited to disease of the spinal cord, as is occasionally the case in patients with multiple sclerosis. Sensory level, root pains, partial or complete intraspinal subarachnoid block, and an unusually high spinal fluid protein are features of intraspinal tumor rarely or never seen in multiple sclerosis. Myelography should always be carried out when these aspects are prominent. Cervical myelopathy associated with spondylosis of the cervical spine (hypertrophic osteoarthritis with degeneration of intervertebral disk and calcified ridge formation),[101,102] platybasia, and other congenital malformations (Arnold-Chiari) are disorders producing mechanical injury to the cord with a clinical picture simulating that of multiple sclerosis. Assistance in their differentiation is provided by x-rays of the skull and spine, myelography, and pneumoencephalography. The older age group in spondylosis, the younger

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age incidence of platybasia and Arnold-Chiari malformation and the more static course in all three contrast with the usual picture in multiple sclerosis.

Diffuse degenerative and more generalized types of primary demyelinizing diseases of the central nervous system can easily be mistaken for multiple sclerosis. Subacute combined degeneration of the spinal cord is identified by the coexistence of primary macrocytic anemia or achlorhydria, signs of peripheral neuropathy, and dramatic response to vitamin $B^{12}$ or liver extract when treated early. The hereditary spinocerebellar degeneration, Friedreich's ataxia, begins far earlier than the majority of cases of multiple sclerosis, presents a more symmetrical diffuse picture, and progresses more steadily. The various syndromes of diffuse sclerosis affecting predominantly the subcortical white matter of the brain (Schilder's disease and variants named after Pelizaeus-Merzbacher, Balo, Greenfield, Krabbe-Scholz, and others) are characterized by progressive intellectual defects, convulsions, blindness, and ultimate profound mental and physical deterioration. Some of these progress rapidly downhill to death, occurring commonly in infants, children, and juveniles (Schilder's disease). Others occurring in adults may go on for many years. There is no specific laboratory identification of these disorders and in the more prolonged states differential diagnosis from multiple sclerosis is difficult during life and must await post-mortem examination.

Systemic diseases secondarily affecting the nervous system may transiently mimic multiple sclerosis. In the collagen diseases such as polyarteritis nodosa and lupus erythematosus, fever, increased sedimentation rate, leukocytosis, eosinophilia, and visceral involvement (pulmonary, cardiac, and renal) usually provide an explanation of the true nature of the neurologic manifestations. Manifestations of these diseases include evidence of muscular and peripheral nerve involvement in contradistinction to the exclusively central nervous system involvement in multiple sclerosis. Central lesions, however, producing paraplegia, hemiplegia, diplopia, and nystagmus have been infrequently described[103] and may occur before systemic manifestations are severe, thus raising the question of multiple sclerosis.

The blood disorder, sickle cell anemia, may also produce recurrent symptoms and signs of disseminated central nervous system involvement, including vertigo, visual impairment, hemiplegia, cranial nerve dysfunction, and sensory defects. The occurrence of pain, fever, visceral enlargement, anemia, and sickling of the erythrocytes, provide ready clues to the primary process. The occurrence of repeated attacks of neurologic symptoms and signs in young Negroes, in whom multiple sclerosis is less common, should arouse suspicion of this disorder.[104,105]

## TREATMENT

There is no reliable preventive measure or effective therapy for the basic disease process. These facts are not surprising in view of the absence of knowledge of specific etiology and mode of pathogenesis. Nevertheless, numerous semirational methods of treatment based on theories of causation, and empiric methods based on alleged favorable results have been applied with the hope of ameliorating the course of the disease. One category of therapeutic measures

includes those directed toward relief of the various symptoms of the disease. Another group of treatment measures has been concerned with counteracting the complications of multiple sclerosis.

A number of difficulties have arisen in the interpretation of the results and therefore in judging the value of the different therapies directed to the specific disease process: (1) During the earlier stages of the disease, when the condition is apt to be acute and remittent, spontaneous reversibility of symptoms and signs makes it almost impossible to determine the role of concomitant therapy in any improvement that occurs. (2) After the disease has progressed to some extent, in the later stages, gliosis and permanent destruction of nerve fibers in the brain or spinal cord represent a pathologic state which is, according to present knowledge, unmodifiable by any form of treatment. It is thus evident that the chief criterion of therapeutic efficacy needs to be largely that of prevention of further progression of the disease. (3) Psychologic peculiarities inherent in patients with multiple sclerosis and even in their families, who appear to be unusually strongly motivated to seek help and to try new therapies, make reliance on statements of subjective improvement quite hazardous in judging therapeutic benefit. Often it is this type of evidence that has been cited in reports. (4) The establishment of satisfactory criteria for determining improvement or cure has been most difficult. (5) The goal of studying sufficiently large groups of patients treated with given methods over sufficiently long periods of time to attain statistical validity of data obviously presents great obstacles.

In the attempt to approach this problem more objectively, prognostic indices have been worked out to assist in the prediction of the future probable spontaneous course of a patient's illness. These are on the basis of age of onset, previous course, duration, present age, and status.[71,106] In addition, scales have been created and criteria set up on the basis of which the total neurologic dysfunction or disability status could be scored in terms of numbers or categories providing greater ease and simplification of comparison of the patient's condition at different times.[107,108] It is doubtful, however, whether the application of these statistical methods provides any sounder basis for determining whether a given change for the better in a patient is due to the treatment he is receiving or represents a spontaneous fluctuation in the disease. The nature of the improvements that have been described in relation to various treatments has concerned the apparent halting of a slow steady progression of the disease, an alleged actual lessening of the total amount of disability, i.e., improvement in the state of general neurologic dysfunction long present, the more rapid clearing of a fresh episode than would be expected naturally, and the prevention of recurrences or subsequent relapses.

Therapy directed theoretically toward the specific disease process will be taken up first. Following this, symptomatic treatment and the management of complications will be discussed.

*Therapy Directed Against the Central Nervous System Lesion.*—Most of the primary therapies have had as their aim the prevention or counteraction of hypothetical mechanisms of pathogenesis through improvement of circulation to the nervous tissue, enzymatic support of tissue oxidation and metabolic func-

tions, provision of substances to make up for alleged nutritional deficits, interference with possible allergic reactions, or through counteracting possible toxic or infectious agents. These approaches to therapy will be briefly reviewed, but for more detailed accounts of the methods, accompanied by bibliographic references to the original reports, the reader is referred to critical reviews published elsewhere.[109a,b]

*Vasodilators:* The basis for vasodilatation as a therapeutic method has been the assumption that lesions may be caused by localized vasoconstriction. Histamine by subcutaneous or intravenous administration, as well as by absorption through the skin by iontophoresis, has been extensively used but is less in vogue than formerly. No agreement has been reached on its value. In the favorable reports, the type of improvement has been that which might be expected to occur spontaneously, whereas lasting benefit and material modification of the long-term course of the disease has not been shown.

The intravenous injection of tetraethylammonium chloride (TEAC), a sympatholytic agent producing profound vasodilatation and postural hypotension, was given extensive trials in large numbers of patients, intravenously and intramuscularly. Lack of evidence of sustained or long-term improvement has led to discontinuance of this form of therapy.

In the past several years a series of clinical investigations on the use of strategically timed acute vasodilatation has been reported as showing favorable effects on fresh symptoms or new signs.[110] The method, called "relief by flush," has been alleged to be capable of providing remission of the majority of symptomatic phenomena of not more than 10 months' duration. When the symptomatic phenomena were of not more than 6 weeks' duration, the improvement was maintained at a fixed level after therapy in 90 per cent of the cases. Agents recommended are amyl nitrite (up to 6 inhalations at a time), inhalation of 5 to 10 per cent carbon dioxide in oxygen with rebreathing at the rate of 3 liters per minute for 10 minutes, and histamine phosphate (1 per cent) given by iontophoresis until a flush of desired intensity is reached. Such therapies are repeated at variable intervals depending on the course of symptoms. The techniques suggested require virtually constant supervision of the patient during acute phases and readiness to apply therapy at a moment's notice throughout the 24-hour period. No confirmation of the favorable reported results has been published by other workers.

*Anticoagulants:* The effect of the continuous daily oral administration of Dicumarol has been reported with both favorable and unfavorable conclusions. An early study suggested that in the remittent form of multiple sclerosis it was effective in preventing further relapses. The rationale for anticoagulant therapy in the treatment of multiple sclerosis, based on investigations supporting the occurrence of scattered venular thromboses in the pathogenesis of lesions, has been debated. Because of attendant risks and long-term impracticability, the method has not been generally adopted as a routine treatment for multiple sclerosis.

*Nutritional factors and supplements:* In former years intensive therapy with liver extract, high doses of vitamins, especially of the B group (orally and paren-

terally, including intrathecal) was carried out. In more recent years the intramuscular injection of large doses of Vitamin $B_{12}$ has been applied. Nicotinic acid in oral, flushing doses continues to be popular. No evidence has been presented that vitamin therapy has been of more than general supportive value in multiple sclerosis. The maximal preservation of a good nutritional state with the aid of a high calorie, high vitamin diet continues to be recommended on general principles. Specific vegetable and fruit juice diets proposed in Europe have not come into vogue in the United States.

The high fat diet proposed two decades ago is no longer in use. The results of the more recently proposed low fat diet have been reported as encouraging,[39] but this has not been generally confirmed. Because of the possibility that maintenance and function of the myelin sheath may depend on the specific nature of the fatty acid components of the cerebrosides which it contains, and because of a possibly acquired deficiency of such acids, observations were recently made on the feeding of fatty acids from cerebrosides to patients with disseminated sclerosis.[111] No conclusions could be drawn.

*Metabolic stimulants:* Experimental trials of the administration of adenosine triphosphate (ATP)[112] and adenosine-5-monophosphate (muscle adenylic acid)[113] have been carried out. The investigations were inspired by the known importance of these biochemical substances in intracellular chemistry but without certain knowledge of their pharmacodynamic action. The reports suggesting improvement are inconclusive.

The administration of sodium succinate orally and intravenously over prolonged periods has been reported to produce subjective and objective improvement in the majority of patients,[114] but the value of this therapy awaits further investigation on a larger number of patients over a longer period of time.

The empirical use of commercially available tissue extracts, including deproteinated pancreatic extract (Depropanex) and pancreatic digestive heart muscle (Pancorphen) has been alleged to result in improvement, but the results have not been corroborated by other investigators.

Adrenocorticotropic and adrenocortical hormones have been intensively studied in regard to their therapeutic usefulness and continue to be used in many quarters for the treatment of multiple sclerosis. Discussion of the rationale for the application of these substances will not be attempted in this review. Studies by one group[115] indicated inconsistent results with the conclusion that ACTH and cortisone were not suitable therapeutic agents for multiple sclerosis. Other investigations have also concluded that the value of such therapy was uncertain.[116,117] However, many clinicians still feel that the immediate use of one of these agents during an acute episode leads to a more rapid defervescence of the lesions and symptoms.

*Antiallergic therapy:* Although evidence derived from experimental and pathologic studies has suggested that multiple sclerosis might be due to hypergic tissue reactions in the central nervous system, there is as yet insufficient evidence to indicate that ingestion of foodstuffs or contacts with external substances to which the person is hypersensitive play a role in such reactions. Various measures have been applied, however, to counteract allergic hypersensitivity

including desensitization injections and elimination diets.[55] The results of these therapeutic endeavors have not been sufficiently good to permit unqualified recommendation for general use.

*Chemotherapy:* Over the years many methods of anti-infectious therapy have been tried without success. As already indicated, the infectious etiology of multiple sclerosis remains unproved. Recent trials of the empirical application of isonicotinic acid hydrazide (Isoniazid) were initially reported as showing encouraging results,[44,118] but subsequent studies indicated that the treatment was probably not of value.[119,120] Intrathecal tuberculin has been incidentally evaluated in a preliminary study, but no final conclusions were reached regarding its therapeutic efficacy.[45]

*Miscellaneous therapies:* Two studies have reported therapeutic benefit from whole blood transfusions,[84,121] rationales for which are given in the respective papers describing the favorable results of therapy. Circulatory stimulants have also been proposed and reported as beneficial in overcoming hypothetic "vasoparalytic" vascular phenomena leading to stasis, sludging, and perivascular lesions in the nervous system. For this purpose a variety of vasopressor drugs has been used, inasmuch as vascular hypotension has been found commonly associated with multiple sclerosis. Lack of controls impairs the validity of the impressionistically reported favorable effects.

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## SUMMARY

The majority of studies referred to in the foregoing discussion of treatments directed presumptively against the nervous system lesions suffer from the defect of inadequate control of the methods used so that results reported lack statistical validity. As already pointed out, however, such control is difficult to attain in this disorder. In none of the therapies described has here been a high degree of benefit, uniform or lasting improvement, or significant corroboration by other investigators.

Although it is unlikely that a generally effective or universally applicable specific therapy is available, the point must be born in mind that in each therapy proposed, there may be those who have had actual benefit from the therapy applied. Considering our continued ignorance concerning etiology and pathogenesis, the indefatigable efforts of clinicians to arrive at some solution to the difficult problem of specific therapy on empiric, presumptive, semirational, or rational grounds may be viewed as reflecting the constant striving of medicine to render help to the unfortunate victim of multiple sclerosis despite the severe difficulties encountered in this field. It is therefore reasonable, in order to give the patient every potential benefit, to carry out a trial of one or more such therapies, the selection being dictated by the status of the patient or more or less arbitrarily by the physician.

It should be nevertheless emphasized that once therapies have been shown, after longer follow-up, through repeated endeavors, or under conditions of maximal control, to be valueless, it would seem unfair to perpetuate their use. Whether it is justified to continue to apply therapies which cannot be disproved

to have value in some patients, even though proof of value in others or in all is lacking, remains debatable.

*General supportive and hygienic measures:* Several studies have shown psychotherapy to be of probable value in ameliorating the course of the disease as shown by an apparent reduction in the frequency of recurrent episodes and apparent maintenance of a status of lesser disability.[23,61,122] How this is brought about is unknown, though the prevention of possible pathophysiologic alterations secondary to pernicious emotional reactions, such as vasoconstriction, for example, has been postulated. General morale-building, supportive psychotherapy as well as more specific psychiatric treatment directed toward personality problems and emotional conflicts are often indicated for the well-being of the patient with multiple sclerosis and perhaps may be shown eventually to have more specific value if factors of life stress and attendant emotional factors contribute to pathogenesis. As a background for whatever other measures of therapy are directed toward the patient, the physician should demonstrate willingness to care for the multiple sclerosis sufferer and to preserve an optimistic attitude.

Because first attacks and new episodes seem often to follow upon physical strain, exhaustion, or chilling, the avoidance of these should be sought. Limited programs of activity commensurate with the patient's capacity and tolerance during static or steadily progressive phases, and prolonged rest following new episodes are in all probability helpful in preserving optimal control over the course of the disease. Vigorous treatment of coexistent or intercurrent infections may diminish the possible risk of worsening of the disease or precipitating a relapse. It is doubtful whether removal to a warmer climate is of specific value in modifying the course of the disease except as it represents opportunity for rest and freedom from stresses inherent in the patient's usual situation. The preservation of optimal nutrition by means of a generally well-balanced, high calorie, high vitamin diet has already been referred to.

Operations and general anesthesia should be avoided if elective and not absolutely essential. Certain types of anesthesia (such as spinal and perhaps inhalant with ether) may have a deleterious effect and should probably be avoided. The long-held notion of a deleterious effect of pregnancy on the course of the disease has been cast into doubt by recent statistical studies. On the basis of these reports, pregnancy would not appear to be contraindicated unless the emotional or physical stresses consequent upon subsequent child rearing are great. It is doubtful that pregnancy should ever be interrupted because of multiple sclerosis save where vital functions of the mother are threatened because of an advanced state of incapacitation.

*Symptomatic Therapy.*—Symptomatic therapy will remain the most important aspect of the management of patients with multiple sclerosis until specific curative or preventive measures are at hand. Aid for symptoms of multiple sclerosis is available for motor dysfunction, bladder and bowel disturbances, ocular imbalance, and mood deviations.

*Motor dysfunction:* The motor loss in multiple sclerosis consists of weakness, muscle wasting, loss of functional patterns, ataxia, intention tremor, impairment of fine skilled acts, spasticity, involuntary reflex spasms, and muscle contractures

restricting full range of motion at the joints. Techniques of physical therapy developed to counteract all these phenomena may be used to advantage. In addition, drugs are being introduced, which are effective in counteracting spasticity and reflex spasms.

Physical therapy is of no value for the nonmotor symptoms of multiple sclerosis (visual, speech, sensory, bladder, etc.). It is probably contraindicated in acute phases of the disease where rest would appear to favor reparative processes in the central nervous system. It may contribute to some extent to a slowing of the rate of progressive incapacitation in those cases where a slow steady downhill progression is evident. Its maximal usefulness appears to be in those patients who have residual motor disabilities but are in a relatively static phase of the disease. Gait training, to improve efficiency and safety and help in learning new ways of achieving the innumerable daily acts of living, are of special importance in increasing the independence of such patients.

Drugs to reduce spasticity and reflex spasms continue to be evaluated. Mephenesin (Tolserol) and curare are but little used for this purpose now. Chlorpromazine (Thorazine) and meprobamate (Equanil, Miltown) have been shown to have slight muscle relaxing properties on oral administration. The most recently developed synthetic oral skeletal muscle relaxants, zoxazolamine (Flexin), methocarbamol (Robaxin), chlorzoxazone (Paraflex) appear in some patients to have some effect in reducing spasticity and flexor spasms, but as yet no ideal agent for this purpose is available.

When spasticity is extremely severe with hyperadduction and scissoring of the lower limbs, excessive involuntary flexion spasms, and beginning deformity due to contractures, the likelihood of ever regaining useful function of the lower limbs is remote. In such instances, as a measure of last resort for symptomatic help, surgical intervention should be considered. This may be selective alcohol block or surgical section of lumbosacral motor nerve roots to bring about permanent relaxation of lower limb muscles. Such procedures usually add greatly to the patient's comfort and alleviate nursing problems, though permanent paralysis of the denervated muscle groups must be accepted.

*Bladder and rectal dysfunction:* The lesser degrees of bladder dysfunction such as urgency, frequency, and occasional mild incontinence may be effectively relieved through the use of anticholinergic drugs including the belladonna alkaloids, especially atropine, and the synthetic preparations such as propantheline (Pro-Banthine) and isopropamide (Darbid). Though fecal incontinence is less common than urinary incontinence, these drugs similarly inhibit involuntary rectal overactivity. The more common rectal symptom of constipation has been effectively treated by use of an oral detergent, dioctyl sodium sulfocuccinate (Doxinate, Colace) and mild peristaltic stimulants such as senna derivatives (Senokot) or cascara. Another commercial preparation useful for the latter purpose has been Dorbane. Many patients are able to establish quite regular bowel habits with spontaneous evacuations every second or third day through the help of these agents. In other patients regular bowel emptying is impossible save with the use of regularly given enemas, usually not more often than at 2- or 3-day intervals.

In patients with more advanced disease where there is total loss of bladder control, an indwelling catheter is essential to counteract the damaging effects of chronic urinary retention. The catheter may be attached either to a tidal drainage apparatus, providing a somewhat more physiologic and rhythmic filling and emptying of the bladder, or simply to a dependent rubber drainage tube leading to a reservoir. Rubber urinals strapped to the thigh are quite useful and practical for this purpose if the patient is ambulatory or in a wheel chair. Complications in relation to bladder disturbances are discussed below.

Patients frequently seek symptomatic help for visual disturbances. The impairment of visual acuity due to retrobulbar neuritis cannot, of course, be helped, and patients should be discouraged from repeated refractions and changes of lenses. Diplopia, present as long as both eyes are open, may be eliminated through the use of a plastic eye shield alternately covering one eye or the other.

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Many patients with multiple sclerosis are euphoric and apparently in little emotional distress. Others, however, seem perpetually irritable, dissatisfied, tense, apprehensive, or depressed. The long-term use of one of the newer ataractics is justified if an ameliorating effect on the emotional disturbance is achieved by one of these agents. It should be borne in mind that aside from providing comfort and operating as a symptomatic measure, it is possible that the relieving of pernicious emotional states may be of benefit to the specific disease process itself.

*Treatment of Complications.*—The complications of bladder dysfunction are those of secondary infection, formation of bladder calculi, and obstruction of bladder drainage from encrustation of the catheter. The prevention of these complications may be assisted through daily irrigation of the bladder with 180 to 240 c.c. of 0.5 per cent acetic acid, liberal intake of liquids, the daily administration of an antacid such as a colloidal aluminum gel, and substitution of clean sterile catheters at intervals. The inhibition of the excretion of phosphates in the urine, formation of stones, and encrustation of the catheter has been claimed to follow the use of oral antacids. In the absence of encrustation of the catheter and evidence of acute infection, the catheter may be left in place indefinitely. Regular urinalysis to determine the degree of inevitable pyuria, and culture of the urine especially when there is systemic or local evidence of acute genitourinary tract infection should be carried out, followed by treatment with appropriate chemotherapeutic and antibiotic agents when indicated.

When patients are chair-ridden or bedridden, decubitus ulcers sooner or later become a problem and should be treated by the usual conservative measures, which will often lead to healing. These are avoidance of further pressure, wet dressings, in some instances the application of antibiotic solutions or ointments, in others simply exposure to air followed by dry sterile dressings. If necessary, surgical repair should be carried out, including débridement and grafting.

Though pain is an infrequent symptom in multiple sclerosis, the occasional occurrence of facial pain resembling trigeminal neuralgia demands help. High doses of orally administered nicotinic acid (100 to 200 mg. four times a day) seems in some instances to be associated with relief of the paroxysms. The

response of this symptom to high doses of vitamin $B_{12}$ parenterally has been quite as inconsistent as has been the response of other symptoms of multiple sclerosis. Peripheral alcohol block of the involved trigeminal division as a temporary measure followed by eventual trigeminal root section has been resorted to when pain was persistent and recurrent. Why this should be helpful is unclear.

The complication of acute pulmonary infection is treated in the usual way. In the far advanced patient, aspiration pneumonia or hypostatic pneumonia may be terminal events regardless of therapy.

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# PARKINSON'S DISEASE

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## INTRODUCTION

THE complex clinical state known as Parkinson's syndrome seems today to be an increasingly serious medical problem. It may be of interest to note that James Parkinson[1] himself saw and described but 5 patients in his extensive London practice whereas today any of us who devote special care and interest to this disease will in a few years have a series of one to two hundred. (At the Massachusetts General Hospital in 1939, when we began to work with this disorder, we had 37 patients; in 1957, our Kardex file covers 700, of whom 69 are dead.)

## INCIDENCE

Garland[2] noted nearly 300 patients in a population of half a million in the area of Leeds, England, an incidence of 1 in 1,700. This is close to our own estimate, based on residence and local population density (1 in 1,500). Kurland[2] from the United States Public Health data and careful local checking in Rochester, Minnesota, reaches a higher value, namely 1 in 600 with a higher incidence in the seventh and eighth decades. Since early or very mild cases are not usually known statistically, and others of this sort may not be recognized, we may reasonably estimate that there are between 250,000 to 500,000 parkinsonian patients in the United States.

From a recent (April, 1958) questionnaire sent to 500 of our own patients, we found that 4 per cent reported a case of Parkinson's disease in one of their siblings, parents, grandparents, or offspring. This agrees with other large series as to so-called familial incidence but is at variance with some, reporting it as high as 25 to 30 per cent. We encountered 7 twins in this group. In the case of two of these, the other twin had died in childhood. In none of the surviving twins (3 identical, 2 fraternal) was there any evidence of Parkinson's disease. This suggests that there is little, if any, generic predisposition toward Parkinson's disease. The 4 per cent familial incidence could also be interpreted as evidence

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that 2 members of the same family were exposed to the same causal agent, whatever it may be. We have already noted a 10 per cent mortality in our series over a 10-year period, although death as a direct result of the disease is almost unknown.

ETIOLOGY

In the usual textbook, three types of Parkinson's disease are listed: *post-encephalitic*, *idiopathic*, and *arteriosclerotic*. Many patients developed Parkinson's disease following encephalitis lethargica during the world-wide influenza epidemic of 1917-1919. This seemed at the time to affect all age groups who developed any form of encephalitis as a complication of the influenza virus infection. Patients with Parkinson's disease who had no encephalitis were classified as *idiopathic*, and those whose symptoms appeared when elderly were called the *arteriosclerotic* type.

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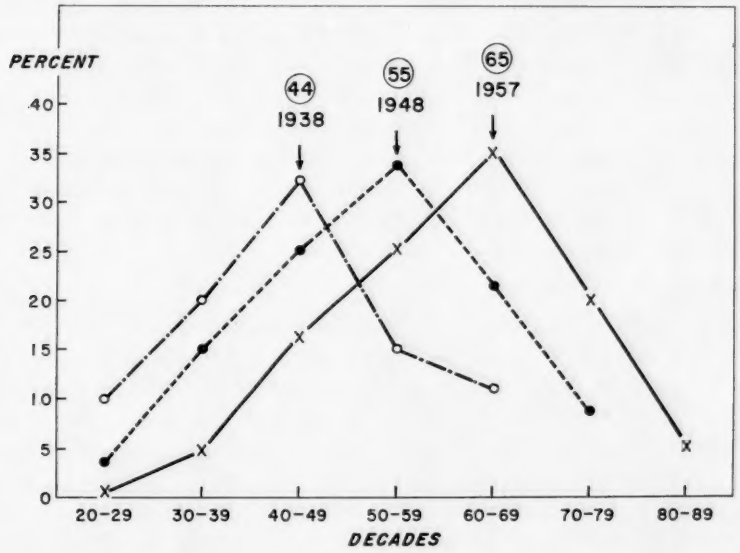


Fig. 1.—Age distribution curve for a combined series of Parkinson patients from New York, Leeds (England), Boston, Kassel (Germany), and Buenos Aires (Argentina), for the years 1938, 1948, and 1957. This shows the gradual increase in the peak age in each of the decades. There is both a dropping off of the younger patients and an increase in the elderly ones in each group.

Schwab and associates[4] have shown from the combined Boston, Leeds, and New York series, supplemented by several hundred each from Argentina and Germany (1,600 cases in all), that there has been a steady yearly increase in the average age of the patients seen in any particular year (Fig. 1). For example, the average age was 44 in 1938; 55 in 1948; and 65 in 1957. In 1957, patients under the age of 40 were indeed rare, as were patients in their seventies in 1948.

This suggests that the group as a whole is growing older, and their disease has a common cause such as the influenza epidemic. In our own cases, 60 per cent recollect an infection with this "flu" and only one of our patients was born after 1927. We know that the interval between encephalitis and Parkinson's disease was shortest in the most severe cases, developing sometimes directly as the somnolence and fever subsided.

The mildest cases, with no neurologic components recollected at all, would seem to have had latencies of 25 to 30 years, if this factor is indeed etiologic. One can also raise the question of a metabolic cause, possibly in the disturbance of trace metals, such as manganese. We know that poisoning from this metal produces a severe basal ganglia syndrome resembling Parkinson's disease. Manganese is a common *trace* substance in most diets, but whether we can associate this disease with a metabolic imbalance or find that a previous virus infection years before predisposes the patient to a metabolic disaster remains a challenge for the future.

Since the parkinsonian population is now clearly older and well into the geriatric group, it would seem logical to look to arteriosclerotic changes as a cause, one advocated by Critchley,[5] in 1929. This, however, does not seem tenable for the following reasons. Most patients with concomitant cerebrovascular degeneration and Parkinson's disease have had some of the early Parkinson symptoms well before any vascular changes could be expected or were apparent. Furthermore, severe cerebral arteriosclerosis in many forms produces no Parkinson symptoms whatsoever. It is true that a mild Parkinson's patient becomes worse with the slow development of hypertension and atherosclerosis, but whether this can be called etiologic is not clear.

PATHOLOGY (ANATOMIC AND PHYSIOLOGIC)

The pathology of Parkinson's syndrome has received meticulous attention in the first half of this century. In 1942, Benda and Cobb[6] presented a summary of most of this work, to which little has been added. The early extensive studies of Foix and Nicolesco,[7] Bielschowsky,[8] and Hassler[9] are now classic. Denny-Brown,[10] Wolf,[11] and Greenfield[12] have recently reviewed the literature. There appears to have been no really new development in this field in the past 10 years. The "amyloid" bodies often noted in the cells of the substantia nigra and brain stem, described in some cases by Lewy and emphasized by Greenfield, may have some specific significance. It is agreed that in the true postencephalitis variety of the syndrome a more prominent abnormality will be found in the substantia nigra and locus caeruleus than in the "idiopathic" variety. Grossly, the black nigral crescent is strikingly pale in comparison to the normal one (Fig. 2). Microscopically here, as well as in the pallidum, there are cell necroses, neurofibrillary change, scarring, gliosis, and certain amounts of lacunar development. Lesser amounts of this pathologic process may be expected in varying degree from the cerebral cortex itself down to the medulla in severe forms (especially the locus caeruleus inferior olivary nucleus and dorsal nucleus of the vagus). In mild so-called idiopathic cases that come to post mortem from other causes we may see only partial cell loss in the mesial substantial nigra, and midbrain reticular areas close by.

Advances in understanding of a clinical disorder have often originated in a precise appreciation of the underlying pathologic process. In the case of Parkinson's syndrome, however, pathologists appear perplexed in their efforts to cast further light on the condition. Heath,[13] in a critical review, found this subject discouragingly variable; Greenfield[12] even wrote that he believes it unlikely that classic pathology has more to offer in the delineation of Parkinson's syndrome. He suggests that the next step forward will have to come from some other source.

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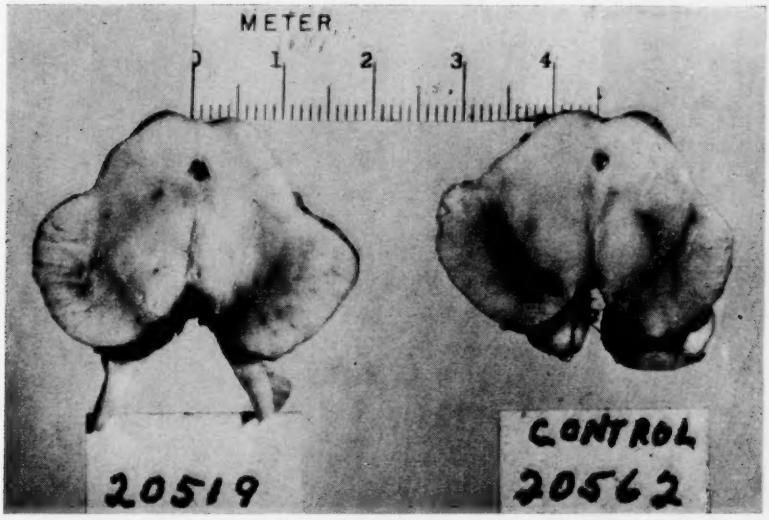


Fig. 2.—Gross section through the substantia nigra (midbrain) of a patient who had bilateral postencephalitis Parkinson's disease (left of figure), and a non-Parkinson midbrain with normal pigment in the nigral region (right of figure).

Note the almost complete disappearance of pigment granules particularly in the left substantia nigra of the patient and marked reduction of pigmentation on the right side. There is slight dilatation of the aqueduct in the Parkinson patient which is in accordance with the enlargement of the third ventricle in this case. (Courtesy of Dr. E. Pearson Richardson, Jr.)

In the past 20 years, much pertinent neurophysiologic work has been presented. Varying qualities of tremor, a cardinal phenomenon in this disorder, have been produced by different specific brain-stem lesions. Ward, McCulloch, and Magoun[14] first described a resting alternating tremor produced by lesions of the dorsolateral and ventrolateral mesencephalic and pontine tegmentum. Later Jenckner and Ward[15] presented "a rhythmic alternating peripheral movement" in monkeys, produced by high-frequency stimulation of the medial reticular formation of the brain stem from a level rostral to the red nucleus down to the pyramidal decussation. The precise description of this movement "analogous to tremor" (with a higher frequency than that of Parkinson's syndrome) is admirable in a field where the tendency to uncertain terminology is common.

This tremor was abolished by drugs, especially scopolamine and diethazine (Diparcol). Jenckner and Ward[15] were actually able to titrate the effectiveness of antitremor drugs in their preparation. They presented a theory that in this region where tremor probably originates the nerve cells might be partially denervated and hypersensitive to acetylcholine. They noted in this relation that medicines for Parkinson's syndrome are all more or less anticholinergic. It has not been elucidated exactly why a tremor appears with the various lesions; it does seem reasonable to believe that damage to the dorsal or ventrolateral tegmentum accounts for a tremor probably identical to that of the clinical syndrome. "Intention," "action," or "cerebellar" tremor is only rarely associated

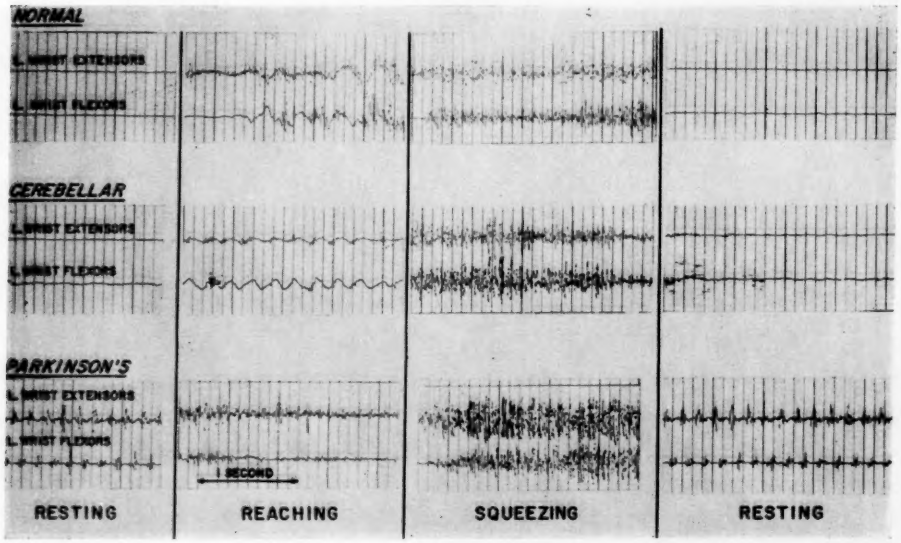


Fig. 3.—Surface electromyograms, inkwriter, of a normal subject, a patient with cerebellar intention tremor and a patient with Parkinson's disease. On the left the 3 electromyograms are shown in the resting and relaxed state. Note that there is no electrical discharge in either the normal or the patient with cerebellar disease, but the patient with Parkinson's disease has the characteristic 4 per second alternating regular tremor at rest.

The next column shows the comparative electromyograms with the subject reaching for a rubber bulb which he will squeeze. The normal has a complicated discharge of flexors and extensors after a brief period of silence in the flexors. The patient with cerebellar disease has the regular 3 to 4 per second intention tremor during the motion. The Parkinson patient has lost his tremor during this voluntary motion and shows a continuous discharge in both muscles without the complex differences of the normal.

The third part shows the squeezing. Here there is no real essential difference between the normal and the cerebeller patient. The Parkinson patient, on the other hand, shows more discharge in the extensors which should be holding the wrist in position than in the actual moving muscle, the flexors. This inefficient use of muscular power is one of the causes of fatigue in Parkinsonism.

The fourth section shows the resting EMG which has essentially the same characteristics as the first resting part with the tremor in the Parkinson person present and silence in the normal and patient with cerebellar disease.

This figure was prepared by Robert S. Schwab for the textbook: Physical Diagnosis, edited by Dr. F. Denny Adams, to be published in 1958, by Williams & Wilkins. It has been reproduced with permission of the author and the publisher.

with Parkinson's syndrome. Magoun[16] speculates that an interplay of impulses from reticulospinal tracts on spinal motor neurons may be of significance.

Schwab[17] noted that in Brussels in discussing Granit's paper the tremor rate of 5 per second was just half the discharging rate of 10 per second in the corticospinal tracts. He suggested, therefore, that disturbances from the midbrain reticular activating system affecting Granit's gamma system might render *alternate* groups of flexor and extensor alpha motor neurons hyperexcitable. If this occurs with the pyramidal tract only slightly active and the subject quite alert, the resting tremor would appear and disappear (as we know it does) with the more active pyramidal innervation accompanying voluntary movement (Fig. 3). It would disappear, also, as the reticular activating system subsided, with relaxation and drowsiness.

The plastic type of ridigity, cogwheeling, loss of associated movements, expression, etc., seen in this disease have been produced by both Ward[18] and more recently by Schreiner[19] in monkeys along with the tremor produced by mesencephalic lesions.

Chlorpromazine, prochlorperazine, and reserpine are able in large doses in man to produce the rigidity, tremor, and other signs of Parkinson's disease. These phenomena slowly disappear on drug withdrawal. We can, therefore, look forward to experimental intracerebral local applications of these substances in the monkey, as for example, in the specific areas where electrolytic lesions are already known to produce tremor and rigidity. This should result in a better understanding of the neurophysiologic pathology of Parkinson's disease.

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## CLINICAL SIGNS

The disease often begins in a very subtle and obscure manner so that in some patients a date of onset is most difficult to determine. A subclinical loss of accustomed dexterity in a hand, for example, may precede the first-noted finger tremor by many years. Such a change might relegate an expert golfer to mediocrity, but otherwise be unnoticed. A peculiar unilateral fatigue in one leg may precede any sort of noticeable shuffle in that foot by 2 to 4 years.

In 20 consecutive patients seen repeatedly by one of us (R. S. S.) we were able, by careful questioning, to "push back" the date of "onset" (as determined by the first appearance of the tremor) by an average of 7 years. Tremor (50 per cent) and noticeable stiffness and rigidity (30 per cent) are reported by most patients in routine histories as the beginning of their trouble.

EXAMPLE.—A 74-year-old, expert shingle roofer, first noted tremor in his left hand 3 years before in a clinical setting of hypertension and generalized vascular disease. This forced him into complete retirement. He later recalled severe influenza with visual complications 31 years before (1918). Ten years after this attack, while rapidly nailing shingles, he was embarrassed and annoyed to note that he hit his nail-holding left thumb and forefinger frequently, because letting go was difficult. He cleverly adapted a new technique so he could continue his job. Five years later (1933), on two occasions, he could not quickly release to a companion a tool from his left hand on request, and was taunted for this. In 1940, his observant wife, and later, his son, noted loss of swing in his left arm on walking. In 1945 (4 years prior to first noting the tremor on the left), his employer criticized him publicly for obvious clumsiness with his left hand in manipulating his roof security devices.

We would list as early signs:

1. Peculiar and occasional involuntary posture-holding in a hand
2. Slight loss in usual dexterity with previously learned motor skills without known cause
3. Vague but consistent unilateral fatigue or feeling of awkwardness
4. Loss of usual vitality in facial expression, often unilateral
5. Loss of usual arm swing on walking
6. Generalized slight slowness in otherwise rapidly executed tasks such as shaving or dressing
7. Slight reductions in usual motor activity such as involuntary head scratching, toying with tableware, and loss of motor habits such as evening walk, etc.
8. Shifting such tasks as sorting mail from one hand to another for no apparent reason

The better known and classical symptoms might be subdivided conveniently into five groups:

A. Involuntary disturbance in the peripheral motor system
   1. Resting alternating 4 to 5 per second tremor
   2. Resting plastic rigidity especially in wrist with cogwheel on passive motion

B. Disorder of voluntary motor movements including efficient, cooperative, associated, and synchronous learned motor patterns
   1. Loss of arm swing in walking
   2. Loss of extension of wrist with grip
   3. Loss of dexterity in fine finger movement
   4. "Petit pas" or shuffling small steps
   5. Festination phenomenon
   6. Pulsion tendencies both in resting postures and while moving
   7. Difficulty in initiating movement
   8. Difficulty in releasing movement ("freezing")
   9. Akinesia in all forms
   10. Marked subjective fatigue and apparent weakness
   11. Postural flexion (hip and neck)
   12. Micrographia
   13. Loss of involuntary limb and muscle shifting (movements of inattention), fixture of posture, edema of feet

C. Disorders or loss in cranial nerve function involving so-called midline or axial movements
   1. Involuntary crisis such as *Oculogyric*
   2. Blephorospasm
   3. Increase of glabellar reflex
   4. Loss of spontaneous blinking
   5. Loss of spontaneous swallowing
   6. Dysphonia beginning with a flattening of clear speech down to inaudible whisper, or even a complete inarticulate state
   7. Loss of associated facial expressions with emotion, speech, and attention, which in severe cases resembles the catatonic stare
   8. Dysphagia in all forms
   9. Sialorrhea both when asleep and awake. This drooling of saliva is not due to excessive production, but to loss of automatic swallowing. It is one of the most annoying symptoms to the patient and deprives his alimentary tract of necessary lubricant fluid, causing constipation (see section under Therapy)

D. Disorders in autonomic nervous system
   1. Greasy skin
   2. Excessive perspiration
   3. Constipation (see C-9)
   4. Urinary urgency, incontinence, and retention
   5. Palpitation, tachycardia, hypertension
   6. Obesity or marked weight loss
   7. Sleep or temperature disturbances

E. Psychic disorders
   1. Specific compulsion, tics, spasms, grimaces
   2. Change in personality
   3. Loss of cognitive function, memory, organizing ability, ambition, drive, judgment
   4. Restlessness, depression, agitated state, excessive anxiety, excessive dependence
   5. Psychotic symptoms, such as pathologic suspicion, hallucinations, delusions
   6. Loss of ordinary motivation
   7. Deterioration of social values, incontinence, carelessness of attire, indifference to others, overdemandingness
   8. Somnolence, excessive yawning, dullness, apathy, partial pseudocatatonia
   9. Mental disorganization, disorientation, confusion, dementia, and amentia

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This partial list of 40 separate symptoms indicates the diffuseness and complexity of some of the advanced and long-standing cases and the difficulty in attacking this disease with one drug or one surgical lesion. For example, a mildly involved patient might have only right-sided A-1 and -2 to a ++ degree (++++ being severe and 0 being normal), with slight B-1 and -3, and some C-4, and nothing in D or E. On the other hand, a severely involved institutionalized patient with long-standing disease would have A-1 and -2 +++ with nearly all of B and C units, especially C-5 and -6, as well as several D and E manifestations. We can do something therapeutically for the first case; we can do nothing for the poor unfortunate second case.

## DIAGNOSIS

As previously stated, 80 per cent of patients date the onset of their Parkinson's disease to the first appearance of a tremor, usually in the fingers, or a specific awareness of stiffness and rigidity in the same area. In the early diagnosis of the disease, we listed a number of preclinical signs or symptoms that might, if they were elicited in the history, lead one to suspect the diagnosis. Usually when the specialist or general physician is dealing with a patient who has Parkinson's disease the syndrome is more advanced, and it is rare indeed for the preclinical or very early signs to be brought to the attention of the physician. Indeed one would hesitate to make a clinical diagnosis of parkinsonism where there was only a very slight amount of subjective awkwardness in one hand and no other signs. One might keep an eye on such a patient for some years and keep in mind the possibility of this disease developing into frank and overt parkinsonism later, since some of us have had this experience. It is important when

a patient presents himself with a story of being bothered or embarrassed by a tremor of the left hand, for instance, particularly when his is under some tension, that this tremor be of the type that is consistent with a parkinson one. The tremor of this disease is characteristically a tremor of rest (Fig. 3). When the hand is lying in the lap, as the patient recounts some dramatic incident in his medical history, the physician may notice that this resting hand begins to shake. The tremor is 4 to 5 per second, and it is a to-and-fro or flexor-extensor tremor and may be either fine or coarse in its amplitude. In early forms of the tremor it tends to disappear for several minutes with change in posture of the hand, and then reappear. As soon as the hand is voluntarily moved in a motor act, such as reaching into the pocket or touching the lip, the tremor will disappear (Fig. 3). In contrast to this, one must note that the so-called tension or intention tremor associated with cerebellar disease is quite different; here there is no tremor when the hand is at rest, even under emotional tension. When the limb is moved, for example, in bringing a spoon to the mouth, the tremor appears and becomes increasingly more intense as the motor act nears completion (Fig. 3). The tension tremor also disappears when at rest and is brought out by extending the arm and by voluntarily tensing both the flexor and extensor movements. One common factor in both the Parkinson resting tremor and the cerebellar type of tremor is that they are clearly intensified during emotional stress. As far as we know, emotional stress will not produce such tremor but will bring them out from the latent state so that they are quite noticeable. Indeed this is one of the mechanisms by which emotional stress of a severe sort (such as receiving news of a death of a son) has erroneously been considered an etiologic factor in Parkinson's disease.

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For example, a physician with this disease stated that the first time he noticed the tremor in his right hand was when he was trying, unsuccessfully, to enter the vein of a crying child in the child's home in the presence of the parents. This would be an embarrassing and stressful situation to any physician. The explanation, of course, is that the tremor was latent and had not been previously noticed either by the patient or his relatives and had been exaggerated by the stress to a level of perceptibility.

The second most common symptom in parkinsonism is the plastic type (so-called cogwheel) rigidity encountered first and earliest in the wrist joint. A patient presents himself with the diagnosis of parkinsonism and states that his wrist feels stiff. If the physician will take the patient's hand and ask him to relax as much as possible, then passively extend and flex the wrist, he will feel this resistance and detect the cogwheeling therein. The other joints, for instance, the elbow, knee, and ankle must be examined also, and may well show, in some patients with long histories of the disease, this same phenomenon. The spasticity of pyramidal tract disorder is quite different from this Parkinson rigidity and the cogwheeling phenomenon is usually not present.

Along with the tremor and rigidity, the loss of associated movements can lead to an exact and early diagnosis. When the patient is walking with his arms unencumbered, the normal easy swing at each step, which involves flexion at the shoulder and elbow, is markedly reduced or lost. Indeed, the arms may be

held in a semiflexed position and adducted over the abdomen. If one is not certain of this loss of associated swing, one can ask the patient to swing both of his arms voluntarily, and it will be noted rapidly that the involved one turns to a fixed position very quickly. A simple test to bring out this loss of swing in the presence of rigidity is to have the patient stand in front of you as relaxed and quietly as he can. Then place each of your hands on his shoulders and gently twist him to and fro at a rate of approximately two times a second. The normal subject, if he cooperates in his relaxation, will show that both arms swing, shoulders, elbows, and wrists in a loose and easy way that reminds one of a doll. The patient with early signs of Parkinsonism will show reduction in this swing usually on both sides, and it may be markedly reduced or absent on the side involved earliest to the greatest degree.

Loss of facial expression, particularly on one side, is not too easy to be certain of in very early cases, particularly when a patient or his relatives insist that he has always been taciturn or phlegmatic in his appearance. However, in watching the patient when he is giving his history, one becomes convinced if there is a unilateral loss of facial expression. One can confirm this by watching the eyes. The normal person in such conversation will blink his eyes between 12 and 20 times a minute. The patient with early parkinsonism will have his spontaneous blinking markedly reduced so that in a minute's time the eyes may blink only 2 or 3 times. Along with this loss of automatic blinking, an exaggerated sensitivity to tapping over the bridge of the nose with one's finger is an early sign of Parkinson's disease. This is called the glabellar reflex, and it must be done by reaching over the patient's scalp so that he doesn't see the finger striking his forehead (which would cause him to blink for another reason). The Parkinson blink will occur with the gentlest tap, whereas in a normal person it takes a considerable effort to produce one. Kinnier Wilson felt that this was a sign found mostly in postencephalitic patients. We have not confirmed this and have found it in all groups of patients.

After one has found some of the above-mentioned signs, others described in the previous paragraphs can be looked for and will probably be found in patients who have slightly advanced forms of the disorder. Actually, Parkinson's disease is probably a rather easy diagnosis to arrive at if one is careful to look for the cardinal and most important signs just described. In our own experience, the errors in diagnosis have largely been in identifying the cerebellar tremor as a Parkinson tremor or misidentification of the spasticity of pyramidal tract lesions for the rigidity of Parkinson's disease.

For the past 7 years, we have placed great weight on the characteristic fatigue curve on once per second voluntary squeezing of a rubber bulb (bulb ergograph) (Fig. 4). It is not necessary, however, to have any kind of elaborate apparatus available, and one can obtain the same kind of a result by having the patient open and close his hands rapidly 20 times. A normal person can do this without too much difficulty, and the amplitude of the muscular movement will remain about the same. A Parkinson patient, on the other hand, tends to show progressively smaller movements so that at the end he is moving his fingers hardly more than a fraction of an inch. The electromyogram in the case of Parkinson's

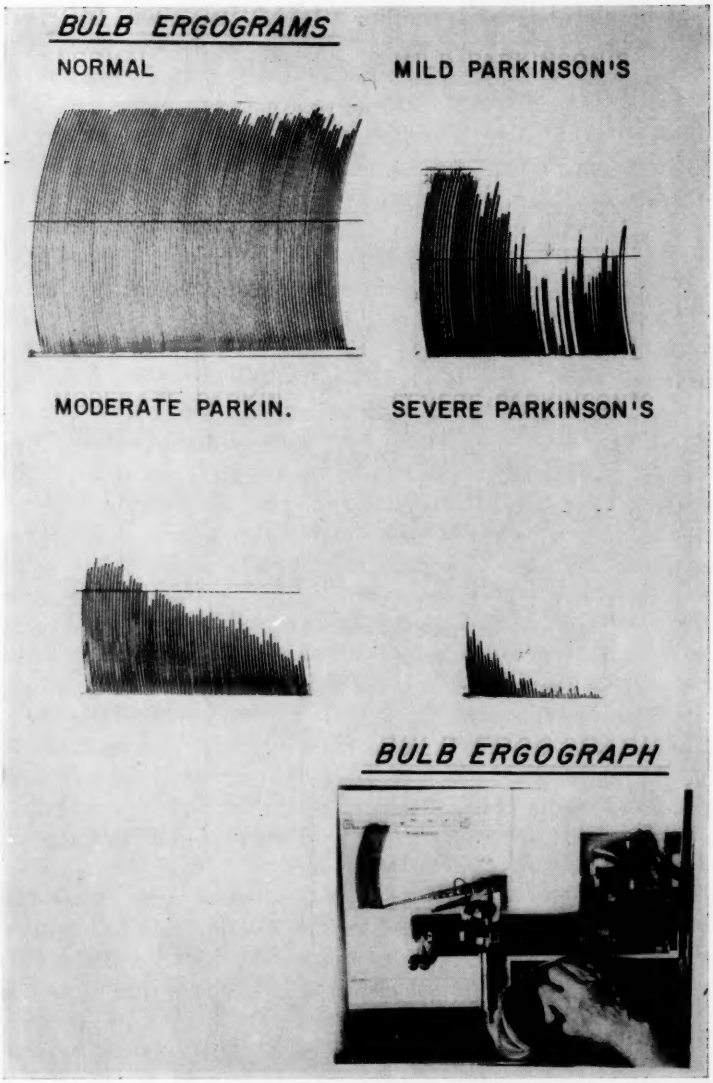


Fig. 4.—Example of a bulb ergogram of a normal subject which is on the upper left showing no fatigue and a normal, continuous high excursion. On the upper right is a person using the same apparatus with mild parkinsonism showing a slow fatigue curve. At the end of the fatigue curve the patient is requested suddenly to do a vigorous squeeze and does so without difficulty showing that the muscle apparatus is not tired but that the motivational voluntary system is the cause of the apparent fatigue at the right top.

At the lower left is a moderately severe Parkinson's disease with a steady fatigue curve. At the lower right is a severe case of Parkinson's disease with very little bulb ergograph performance. One should compare the severe Parkinson performance to the normal to get an idea of the severe motor disability present.

At the lower right is a severe case of Parkinson's disease showing a marked reduction in the bulb ergogram.

At the bottom of the picture is a photograph of the ergograph used which may be obtained through the Harvard Medical School Machine Shop, Mr. F. J. Christensen.

disease is characteristic. The regularity of the 4 to 5 per second muscular discharge is only one feature of the electromyogram of this condition. The other is the discharge from the antagonist muscle which occurs in between the regular discharge of the contracting muscle (Fig. 3).

Recently in an effort to see how our own patients were faring, the following questionnaire was sent out to 500. Three hundred and fifty have replied, and since it will take 6 months to find out why the 150 have not replied, the conclusions from the replies are, at best, tentatively optimistic.

QUESTIONNAIRE

Mark X in appropriate square for each item after reading instructions.

| ITEM | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100% OF NORMAL |
| 1. Dressing and undressing | | | | | | X | | | | |
| 2. Toilet: bathing, shaving | | | | | | | X | | | |
| 3. Eating foods and fluids | | | | | | X | | | | |
| 4. Retiring, sleep, and arising | | | | | | | X | | | |
| 5. Indoor activities | | | | | | X | | | | |
| 6. Outdoor activities | | | | | X | | | | | |
| 7. Travelling: cars, etc. | | | | | | | X | | | |
| 8. Social activities, conversation | | | | | | | | X | | |
| 9. Business and home activities | | | | | | | X | . | | |
| 10. Personal morale | | | | | | | | X | | |

The above is designed for self-grading of your condition in the following 10 ways. Please enter under each of the 10 items the estimate of yourself, combined with that of your family, indicating the degree or percentage of normal evaluation which would be based on how you were *before you had Parkinson's disease.*

Note that you can use either a score of 0 to 10 or from 0 to 100 per cent. From 0 to 10 per cent (0 to 1) represents such severe incapacity that you are essentially a total invalid, unable to do anything in these categories. Ten or 100 per cent is normal in every way in this category, so that you are no different from anyone else who does not have Parkinson's disease.

The above example indicates a 67 per cent or normal patient from his own reply which would fit into Group III+ which will be described.

1. Dressing or undressing, putting on or taking off overcoats, putting on and taking off ordinary clothes, stockings, socks, garters, girdles, handling buttons, zippers, shoe laces, tying necktie, buckles, and belts. Which of these do you require help in doing?

2. This covers washing, bathing, showers, drying, combing of the hair, tooth-brushing, shaving. Toilet: urination and moving of bowels, wiping and other necessary cleanliness, handling of fly buttons and zippers. Which of these do you require help in doing?

3. Eating foods, using spoons, forks, knives, cutting meat, buttering bread, drinking from glasses, chewing solid food, swallowing, and controlling spilling of food. Eating with other people. Which of these do you require help in doing?

4. Retiring: Getting in and out of bed, turning over in bed, getting comfortable, keeping the covers around you, sleeping, lying quietly on a sofa, being comfortable in a chair.

5. Indoor activities: getting in and out of a chair, opening and closing doors, going up and down stairs, removing or replacing books on shelves, reading, turning pages, playing cards or other games, handling TV or radio knobs, writing, sealing envelopes, etc. Which of these do you require help in doing?

6. Outdoor activities: walking on the sidewalk, crossing the street, moving with crowds, or in automobile traffic, handling of swinging doors, avoiding obstacles, such as stones in a path, or uneven ground. Which of these do you require help in doing?

7. Travel: getting in and out of automobiles, being comfortable during automobile rides, driving your own car, especially in city traffic, getting in and out of buses, trains, and planes, and moving about on the aisles of same. Adjusting seat belts. Any difficulties with seasickness or other forms of motion sickness. Which of these do you require help in doing?

8. Social: willingness and ability to go out calling, seeing friends, or having friends or neighbors in your own home. Going to movies or theater or public entertainment, sports events, being seen in public, attendance at meetings and clubs. Conversation being understood.

9. Business and occupation: keeping up with your former job and estimate as to your value to the organization. If still working full time, ability to keep up to normal; hobbies and recreation. Ability to do housework, chores, bed-making, cooking, dish-washing, sewing, cleaning up. If retired, please mention.

10. Personal morale: Presence of discouragement and depression, feeling that you want to avoid contact with others. Amount of satisfaction in living, and determination to adjust to this illness.

Under items 1, 2, 3, 4, 5, 6, and 7 we have asked you to tell of help you require; for example, in getting on an overcoat. Could you guess or estimate if this help amounts to:

( ) A. Less than 20 per cent, (You do at least 4/5 or 80 per cent of these tasks yourself without aid, even if it takes longer in time and requires more effort on your part.)
( ) B. Between 20 and 50 per cent (You do between ½ and 4/5 yourself).
( ) C. Between 50 and 75 per cent (You do only between ¼ and ½ yourself).
( ) D. Over 75 per cent but not over 90 per cent. (You can do only 1/10 to ¼ yourself).
( ) E. Complete help in all you do,

List appropriate letter A, B, C, D, and E for each of the seven 1, 2. 3. 4. 5. 6. and 7 items if you find an average for all together difficult.

We ran a check on the 10 items by asking for a classification of the total state of performance in one of the six groups.

I. Normal or almost normal—90 to 100 per cent of normal, completely independent.

II. Slightly handicapped—70 to 90 per cent of normal, still independent, but it is more difficult.

III. Moderately handicapped—50 to 70 per cent of normal, slightly dependent in a number of ways, one-quarter to one-third of activities.

IV. Considerably handicapped—30 to 50 per cent of normal, dependent in about half of activities.

V. Severely handicapped—10 to 30 per cent of normal and considerably dependent in two-thirds to three-quarters of activities.

VI. Totally invalided and dependent for everything on others.

We found that only 6 per cent were in Group VI; 20 per cent in V; 20 per cent in IV; 25 per cent in III; 20 per cent in II; and 20 per cent in I. This means that 40 per cent are independent and above 70 per cent of normal and another 25 per cent slightly dependent, making a total of 65 per cent, or nearly two thirds of our group. We believe at present that this is too optimistic and that some shift

downward will result with checking by interview of the questionnaires and seeking our reports as yet unreturned. But it does represent a more cheerful note than we anticipated and reflects worth-while results in our continued efforts to treat, help, and manage these patients over the years. This aspect of Parkinson's disease will now be considered in more detail.

MANAGEMENT

*General Measures.*—(1). Once the diagnosis has been definitely established, the patient, as well as his family, must be clearly informed as to the nature, name, and significance of this disease. Since, at present at least, there is no cure, Parkinson's disease will be a problem for him until death from some other cause. Postponing this interview for a brief period to know the patient better or to bolster a flagging morale, is not unreasonable, but sooner or later the physician must, in language understandable to the patient, inform him of the problem he has to deal with in the future. This is no easy task; it requires both skill and patience. It cannot be hurried and should, of course, be on the optimistic side. To withhold the diagnosis from an intelligent patient for years produces, when the patient accidentally does find out, a combination of resentment and contempt for the doctor which is most unfortunate. The following examples illustrate this point.

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After a lecture in a South American capitol some years ago my host, a professor in the medical school, asked me to see his wife, who had Parkinson's disease. "She doesn't know it—don't tell her," he warned me. I insisted that she must be informed. He finally agreed after an hour's argument. When told, she laughed, "I knew 3 years ago—how stupid could a doctor's wife be—but since he and his friends wanted to pretend, I played the game too."

A business man had the disease for nearly 2 years and was under intensive drug treatment. He felt that his physician did not know the nature of the obscure malady he was trying to treat. When by chance he noted the diagnosis on an insurance form which had been signed by his doctor early in the illness, his resentment and anger were so strong that he came East to see us. He expressed relief that his sickness was a common one and not a mysterious affair limited to a few.

In a questionnaire sent to 250 of our patients, only one replied that she felt her physician, when he was certain of the diagnosis, should have kept it from her. The remaining 249 wished to know, even though this knowledge was not good news. The whole success of proper management and adjustment of the patient depends on cooperative understanding of what this disease means to ordinary living.

A complete medical check-up by the family doctor or by a consulting internist is the next step, evaluating blood pressure, metabolic activity, weight, state of nutrition, bowels, heart, lungs and peripheral vessels, presence of other degenerative diseases such as diabetes, x-rays of the chest, and obtaining any other laboratory studies indicated. Any abnormal findings in these studies must be taken care of as the anti-Parkinson therapy is planned.

Specific plans and instructions in adjusting and adapting to this disease should be discussed. As soon as the diagnosis of Parkinson's disease has been

established and some indication of the amount of disability in motor function is determined along the lines of our questionnaire, the physician can discuss the immediate future with his patient. The essential point here is to describe to him any changes or alterations in his life patterns that might make his adjustment to this disease easy. For instance, patients with a moderate amount of rigidity or tremor find that when they are under the stress of being hurried in doing something (such as dressing or eating a meal) they experience an exacerbation of all of their symptoms and find it frustrating and impossible to finish the task in the allotted time. Therefore, the first adjustment should be one of extending the time scale as far as ordinary chores of life are concerned. More time must be allowed for dressing, washing, shaving, eating, etc.

As far as occupation goes, if it is possible, the amount and velocity of the daily work should be decreased somewhat. An afternoon off in the middle of the week is an essential requirement, early in the adjustment, and leisure, rest, and relaxation on weekends are of great medical importance. Regular vacations should be medical requirements. It is better to take 2 weeks off twice a year than to take one month off at one time. At the same time, one may curtail some of the activities that are associated with hurry and stress. Great emphasis should be made on continuing all forms of normal social intercourse with friends, going to entertainments and games, and travel. Due to the obvious embarrassment of the tremor and the frequent appearance of pseudostupidity because of the lack of facial expression, patients with early parkinsonism are very much inclined to withdraw from their normal social life and remain indoors and at home. Too much pushing on the part of an overambitious spouse, of course, is unwise, but any kind of recluselike existence or restricted life is poor medicine. A reasonable compromise for every problem can be achieved, and a physician's advice in such matters is of great importance.

In the early stages of the disease it is not necessary to develop the use of medical aids, but it may be worth while mentioning some of these at this point. The use of zippers instead of buttons, elastic shoe laces that do not have to be tied, loose clothing (particularly when one is at home) without neckties, open shirts, soft shoes, are all matters of common sense but sometimes are not noted by patients. One of our own patients found that a pair of ordinary bowling shoes was easier to walk with and eliminated scuffle. For those who find cutting meat with a knife and fork difficult, the use of scissors is of great help. Sometimes chairs which are difficult for patients with this disease to get into and out of easily can be made more efficient by increasing the height of the back legs by 2 inches, or by cutting off 1 or 2 inches from the front legs.

Patients who have a great deal of rigidity of the legs and difficulty in walking should have loose scatter rugs removed from the floors since these may cause rather serious accidents from falls. The placement of simple knobs at hand level on the part of the wall next to a door will give the patient something to hold on to when he is opening the latter. Banisters or hand rails should be installed for stairs and the removal of unnecessary bric-a-brac or expensive ornaments from the rooms which a patient inhabits are simple but important measures. All of these things can be discussed with the patient from time to time,

explaining that the secret of success with this disease is complete adaptability to it.

Psychotherapy is the fourth step. Anyone who suddenly finds out that he has a chronic disease for which there is no cure, and to which he will have to adapt his whole life, suffers an emotional trauma. This can be of considerable magnitude. It is particularly difficult to bear for those individuals who have been dynamic, aggressive, and thoroughly successful up to the point of their developing Parkinson's disease. Such people have had, in the past, little sympathy for the chronic invalid and little understanding of what it means. They have gone along under a notion that "it can't happen to me," and they are poorly prepared to adjust to this new onslaught against their security. When such people are informed as to the nature of their illness and the demands that the necessary adaptation will bring out, they sometimes go into a strong reactive depression, becoming thoroughly despondent, convinced that the end has come, that they will be bedridden invalids from now on, and that nothing will be done for them.

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Mild degrees of this reactive type of depression must be, and can well be, handled by the internist or family doctor by a process of gentle suggestion, sympathetic encouragement, and continued reassurance. A sympathetic and understanding spouse makes this task more easy. More severe types of this reactive depression, however, had best be referred to a psychiatrist who has some understanding about Parkinsonism. Sometimes a series of interviews by such a psychiatrist will tremendously build up the patient's understanding and morale and make the task easier for the physician or neurologist. It is hard to say just when one should call on the special psychotherapist. One might temporize for a month by trying every possible ordinary way to reduce the gloom of this reactive depression before consulting a specialist. Sometimes the use of tranquilizers or sedatives helps a little, and these will be described under the pharmacologic therapy of this disease. Where there are a number of Parkinson's patients in a clinic it is economically better and very worth while to have sessions of group therapy for such individuals.[20] One of our colleagues (M. E. Chafetz) has reported on this as an independent observation.

*Specific Therapeutic Measures.—*

*Pharmacotherapy:* There are, at the present time, twenty different preparations which have been advocated for the treatment of Parkinson's disease, and it is obvious that there is no drug among them that will take care of the disease to the degree that insulin does in diabetes. Actually, the best pharmacologic adjustments that one can achieve without side effects is about 25 to 50 per cent reduction of symptoms. The two main symptoms that are favorably affected by such agents at present are rigidity and tremor.

It has long been known that the solenaceous alkaloids such as belladonna, stramonium, and hyoscine have been beneficial in Parkinson rigidity. Since 1947, there have been an increasing number of synthetic analogues of the natural alkaloids which have been found useful in reducing rigidity. Some of the older clinicians still feel that certain of the natural alkaloids are better, if a satisfactory combination can be found, than the newer synthetic preparations. However, this has not been our experience. The three recommended available synthetic drugs against rigidity at present are: Artane, Kemadrin, and Pagitane. Artane

is available in 2 mg. and 5 mg. scored tablets and in an elixir containing 2 mg. per 4 c.c. Pagitane is available in 1.25 mg. and 2.50 mg. sugar-coated tablets. At present, Kemadrin is available only in a 5 mg. scored tablet. One can start with any of the preparations, using the smallest size for the first 3 days, twice a day, then increasing the dose to 3 times a day, and finally, if more is desired, to 4 times a day. It is best to give the medicine during or after meals and to space the doses approximately 4 hours apart. We have not found any advantage in combining drugs, such as Artane and Kemadrin. As soon as side effects, such as dried mouth, blurred vision or, in the case of elderly individuals, nocturnal confusion and loss of memory occur, the dosage must be reduced immediately to a lower level. Continuing these drugs when side effects develop produces increasing mental confusion and later on bladder difficulty, complete urinary retention, and severe obstipation.

The most effective drug against tremor is Parsidol, and this is available in 10 mg. and 50 mg. (scored) tablets. This drug is reasonably effective against rigidity but requires a more careful adjustment than do the three previously described synthetic preparations. One must start with 10 mg. twice a day, increasing to 4 times a day, over a period of 5 days. Then the dose can be increased by increments of 10 mg. using 3 to 5 days as an interval between dose changes. Side effects of Parsidol are drowsiness, dizziness, epigastric distress, forgetfulness, and, in some cases, confusion. It is better tolerated by the elderly patient than are the atropine-like drugs. At the present time it is one of the most effective anti-Parkinson preparations.

Another preparation, Pacatal, is a tranquilizer as well as an antitremor drug. This can be used by slowly increasing the dose, beginning with 25 mg. twice a day, and working up in the course of a week or two to 50 mg. 4 times a day. In this situation it is sometimes quite efficient to combine small doses of Pacatal and Parsidol in the same individual. In some situations where tremor and rigidity are a problem, combinations of Parsidol and Kemadrin, for example, are quite efficient. Such a schedule would be 25 mg. Parsidol 4 times a day and 5 mg. Kemadrin morning and afternoon.

Cogentin, which is an antitremor as well as an antirigidity drug, is more slowly excreted than the others. It is also useful. It comes in double scored tablets of 2 mg. and can be given either twice a day (1 mg. each) or as 2 mg. at night after Artane or Parsidol or some other drug during the day.

A number of patients find that the addition of an antihistamine to the Artane-Kemadrin-Pagitane substances adds to their effectiveness and makes them feel more comfortable. Such an antihistamine as Thephorin 25 mg. along with each dose of the other medicine, or Benadryl 25 mg. along with each dose, or Ambodryl 25 mg. along with each dose of the other medicine can sometimes be used. After a few weeks on this medicine, if the patient yawns a bit and feels sluggish or sleepy, it is quite feasible to add an analeptic such as amphetamine to the morning and noon dose to stimulate alertness. The simplest and best known of these is Dexedrine sulfate 5 mg. per dose. A more gentle one is Ritalin 10 mg. per dose. Sometimes Ritalin can be given in the afternoon without disturbing the patient's sleep. Patients who are extremely agitated, restless,

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and who have difficulty in sleeping must be given sedatives in addition to the anti-Parkinson preparations we have just mentioned.

The problem of sedation in this kind of patient with Parkinson's disease is a perplexing one. Some of them react very poorly to barbiturates such as pentobarbital and are restless in spite of it. We have had fair results with combinations of meprobamate 400 mg., pentobarbital 50 mg., and Benadryl 50 mg. combined as a sleeping potion. Some patients with this condition who are moderate consumers of alcohol find that a glass of beer or a whiskey and soda before they go to bed helps their sleep.

Since chlorpromazine and prochlorperazine in large doses produce, in some patients, Parkinson-like symptoms, they would be expected to increase some of the milder symptoms of a patient who has this disease, and indeed they do just this. Therefore, in our opinion these two drugs, and also reserpine, have no place in the treatment of Parkinson's disease. Pacatal which has been mentioned, is a tranquilizer but is useful because it cuts down tremor. Meprobamate and a few other tranquilizers such as promazine can be used for short periods of time with beneficial results. One would hesitate to recommend any large amount of a tranquilizer in people with this disorder since they usually require stimulants in order to remain alert if they are taking too much of these preparations.

Nearly every one of the preparations mentioned in the foregoing paragraphs increases the Parkinson patient's natural tendency to constipation. Some two-thirds of the patients we encounter have severe constipation as a major problem. In severe cases, this is partly due to the loss of saliva from the drooling at the mouth so that this substance is not available to macerate and soften the food. Another cause is the patient's slowness and awkwardness in motor activity so that the normal draining of fluids is reduced. A third factor is that the drugs mentioned produce slowing of the intestinal tract motions and drying up of the natural secretions. Fourth, the lack of spontaneous movement of the patient with Parkinson's disease tends to produce a generalized inactivity which encourages constipation. All of these factors play some part in producing this symptom, which requires medical handling and supervision.

The first point is to insist on the patient's increasing his fluid intake by drinking at least 5 to 6 glasses of water a day. The use of mineral oil or Petrolagar, mild or even strong cathartics, have many advantages over dependence on daily enemas. A mild Parkinson patient who has to take a cathartic every day is far more independent than one who has to have his spouse or a professional person give him an enema 3 times a week. Our own gastrointestinal consultant has untangled a number of these severe problems of constipation by working out a better diet with roughage and a sensible combination of cathartics.

*Physiotherapy:* The daily use of physiotherapy from the beginning of one's illness would probably greatly benefit most patients. However, there are practical considerations which make this impossible. For instance, a man still in business would find it rather difficult to get to a physiotherapist's office every day for a visit. Furthermore, the economic burden of this type of daily treatment would be difficult for many. We can only recommend that patients with parkin-

sonism get as much physiotherapy as possible. Frequently an efficient physiotherapist can come to the house 3 or 4 times a week, at a convenient time, for a session of 30 to 40 minutes. This is invaluable in keeping the patient comfortable and mobile. The best form of physiotherapy is passive motion and stretching of the most involved muscles and joints rather than massage or infrared treatments or other measures of this type. For instance, in legs which are stiff from the rigidity and in which walking is limited to short "petit pas" so that the steps are only 5 or 6 inches long, the patient would be greatly helped by a physiotherapist who divided her time between strong stretching of the muscles at the hips, knees, and ankle joints to their maximum tolerable and painless extent, and making the patient walk with an increasing length of stride, stepping on some marks on the carpet, floor, or outside, so that he would approach a normal pace. These efforts in gait training and joint stretching are far more effective in our opinion than any form of heat or massage. Most professional physiotherapists (physicians) are aware of this and can instruct the lay therapist as to how to provide these exercises.

A second, and perhaps equally important, phase of the physiotherapeutic program is for the physiotherapist to leave the patient a series of exercises that he can do himself during the day and which could be supervised by his interested spouse. A combination of 3 or 4 times a week of professional therapy with supervised exercises 4 or 5 times a day will keep many a patient far more active and independent than if he has long periods of physiotherapy at less frequent intervals.

Vibrators and hydrotherapeutic units have not proved of any benefit. In about 40 patients we have had some success with an electric rocking chair* which is made through our own clinic and sold at cost to patients. This endeavors to exercise passively, as the chair is rocked by a motor, the ankles, knees, hips, shoulders, elbows, and wrist joints. The success of any exercise program, whether it be with mechanical aids or a physiotherapist, depends on continued daily application.

*Miscellaneous:* One of the problems that face patients with moderately advanced Parkinson's disease is swelling of the foot, usually on the side of the body most involved. At first, one thinks that this is due to cardiac or renal failure, but it is obviously not. Rather, it is due to the patient remaining in a fixed position with his feet on the floor *in the presence of rigidity.* This means that the venous blood in the dependent portion of the body cannot return to the thorax because of the increased peripheral resistance and the absence of the usual pumping action of muscles so that slowly, during the day, as the patient remains in his chair, the feet and legs swell. The only way to overcome this is by exercise or by elevation of the feet for periods of 1 to 2 hours. One may try elastic stockings, but they do not seem to be very efficient and are usually complained of by the patient. Elimination of the rigidity by the proper use of drugs is helpful in many cases and in a few particular instances the use of the electric rocking chair for one-half hour 3 times a day has taken care of the problem completely.

The extreme greasiness and itching of the skin which occasionally bothers patients with this disease can usually be taken care of by application of a drying

*The Electric Rocking Chair Company, 80 Church Street, Lowell, Mass.

wash containing alcohol. Patients with Parkinson's disease, because of the intense dryness of the mouth that often accompanies the use of medicine and the presence, sometimes, of tremors of the tongue, face, and body, do very poorly when their teeth are removed and they have to wear dentures. Furthermore there seems to be some evidence that continued use of these preparations that are useful against tremor encourages deterioration of the teeth. In any case, it is a frequent problem that a Parkinson patient has to face when his teeth become fragmented or infected. Obviously, infected teeth must be removed, but it is strongly recommended that all oral surgeons make every effort to delay this removal of teeth by the use of partial prothesis or special efforts at oral hygiene.

*Neurosurgical treatment:* In the past 10 years there has been an increasingly successful attack by neurosurgeons on the symptoms of rigidity and tremor. In the past 5 years, Dr. Irving S. Cooper has concentrated nearly all of his effort toward this end and has perhaps the largest series of operated patients in the world. Due to the development of successful sterotactic placements within the human brain, and the freedom from infection that antibiotics have made possible, this kind of surgical attack on the problem is far more encouraging today than it ever was. We have very carefully examined[21] a group of patients before and after such procedure so that now we have some 55 subjects that we are familiar with. Our findings are in pretty close agreement to those of other neurologists who have examined and studied these patients. At the present time the operation carries a mortality risk of only 2 per cent and a complication rate of another 2 to 3 per cent. A lesion either in the mesial part of the globus pallidus, correctly placed and of the right size, will reduce the Parkinson rigidity from a level of ++++ to 0 in some patients, or reduce it significantly so that it is one-quarter of what it was before in 80 per cent. Relief of tremor by a lesion in this area has been spectacularly successful in some patients but only partially successful in others. In some 70 per cent of these patients a significant reduction of tremor has resulted. Recently Cooper[22] has found that a lesion in the dorsal lateral nucleus of the thalamus is more successful with reduction of tremor and reasonably successful in the reduction of rigidity. Because there are two places that can now be attacked it is possible, in selected cases, to put one lesion on one side, and one on the other at a subsequent date.

In our experience the ideal patient for this kind of operation is one with unilateral Parkinson's disease whose main symptoms are rigidity and tremor on one side. Such a patient should be well under 65 years of age and show no intellectual impairment or evidence of diffuse brain disease. After a reasonable trial of drug therapy (for example, one year), when it is felt that the penalties of these drugs outweigh their advantages by a significant amount, one can recommend neurosurgery. Successful intervention by the neurosurgeon in such a case will eliminate the tremor and rigidity to such a degree that the patient does not have to take medicine afterward and can go on for many years without serious handicaps due to his disease. However, only *1 per cent* of the total Parkinson population would fit into this category of the ideal candidate.

Patients who show bilateral symptoms and still show no evidence of mental impairment or diffuse brain disease and are not satisfactorily controlled on medi-

cation will be good candidates for this operation provided they are under 65 years of age. The worst side should be done first and a reasonable period of at least 1 or 2 years should elapse before the second operation is considered for the other side.

It is quite obvious, however, that a bilateral case who has his worst side relieved by neurosurgery still has to take medication, although he may not have to take so much. Complications such as hemiplegia, confusional states, and oculomotor palsy occur in this kind of surgery in 2 to 3 per cent, in addition to the 2 per cent mortality already mentioned. This means that permanent neurologic deficits or death may result from this surgery in approximately 5 per cent of the cases. These odds are extremely good compared to the older methods of surgical attack but should be made very clear to the patient before the considers going to the neurosurgeon. It must be emphasized strongly that even when the rigidity and tremor are completely relieved by a successfully placed lesion that the disease is not cured. Reduction in blinking, loss of facial expression, and loss of swing of the arm will still be present in nearly every case, and it is to be expected that in some patients the uninvolved side may sooner or later show signs of Parkinson's disease. Difficulty with speech is not helped by this surgery.

With these limitations before us, however, there is no doubt that in correctly selected patients a type of improvement can be expected from surgery that is never achieved by the drug treatment alone. We estimate that the good candidates for this operation, in addition to the ideal ones, number not more than 12 to 15 per cent of all the patients. That leaves 85 to 87 per cent of all Parkinson patients at the present time to whom one cannot recommend such surgery, and it is this group that consitutes the strong challenge for successful medical treatment and management.

## CONCLUSIONS

An understanding, alert physician, by the careful use of general and specific measures, including neuropharmacology, can bring his Parkinson patients who are in Groups I, II, III, and IV (described above) to levels of improvement of from 20 to 40 per cent above pretreatment levels. He can provide a little improvement, perhaps 5 to 10 per cent, for the patients in Group V who are thoroughly dependent and invalided. He can do practically nothing for the Group VI cases who are totally invalided and fortunately comprise only a small percentage of the whole.

About two-thirds of the patients he will be treating will slowly, but steadily, grow worse over the intervening 5-year period. The other one-third will remain at about the same level or improve a little. The degree of progression is variable and depends on many factors. It is exceedingly difficult to estimate how a person will be 2 or 3 years hence. In general, one can take the rate of progression of the disease before the physician sees the patient and assume that this rate will continue for the next 5 to 10 years, modified slightly by the successful use of drugs. On the basis of replies to our own questionnaire, and subsequent testing, the over-all picture as to what one can do for patients with this disease seems not nearly as discouraging and pessimistic as it was.

The crucial point in any individual patient, however, who consults a physician for treatment of parkinsonism hinges on the complete understanding of the disease by the patient and by the physician. There should be a total attack on the symptoms of the disease by the physician (who should use all of his resources and consultants to employ any useful combination of therapeutic agents) acting together with pledged cooperation by the patient's relatives and by the patient himself.

Until someone discovers a drug or some neurosurgically placed lesion that will take care of all the symptoms of this disease, we shall have to be content with reasonable and partial success in the alleviation of these distressing symptoms.

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# MUSCULAR DYSTROPHIES, POLYMYOSITIS, AND OTHER MYOPATHIES

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THERE has been a recent surge of interest, which is reflected by a growing literature, in diseases of muscle. It is impossible to review the major developments by giving appropriate citations of the literature without a bibliography of major proportions. An attempt has therefore been made to present the present status of thought in this field in general terms.

Because of conflicting terminology, use of the following words has been restricted according to the following definitions:

*Atrophy.*—Any diminution in the bulk of muscle, but in nomenclature it refers specifically to muscular wasting secondary to neural disease (e.g., progressive spinal muscular atrophy, peroneal muscular atrophy).

*Myopathy.*—Any condition characterized by muscular weakness, other than fatigue or emotional asthenia, in which there is no demonstrable pathology of the central or peripheral nervous systems, or the neuromuscular junction. It therefore includes conditions in which the primary defect is believed to be in muscle, such as muscular dystrophies or polymyositis, and may be the only available label for a group of disorders which lack distinctive characteristics. It also includes syndromes of muscular weakness which accompany some generalized metabolic disorder (e.g., thyrotoxic myopathy).

*Dystrophy.*—A myopathy characterized by a pattern of inheritance.

*Polymyositis.*—A myopathy in which histologic alterations of muscle fibers are usually accompanied by a leukocytic cellular infiltration.

*Dermatomyositis.*—Polymyositis with dermatitis.

It is not possible to be rigid about these definitions; the problems involved will be discussed in relation to the specific entities. A tentative working classification of the myopathies is offered in Table I. Those classified as hereditary have a prototype in which familial cases have been found, but sporadic cases in some categories may prove to have more than one etiology.

*Scholar, Sister Elizabeth Kenny Foundation.

TABLE I. THE MYOPATHIES

Hereditary myopathies
- A. Progressive muscular dystrophies
  1. Duchenne type
  2. Facioscapulohumeral (Landouzy-Dejerine)
  3. Limb-girdle
- B. Myotonic syndromes
  1. Myotonic muscular dystrophy (Steinert)
  2. Myotonia congenita (Thomsen)
  3. Paramyotonia congenita
- C. Other varieties
  1. Ocular myopathy
  2. Distal myopathy
  3. Congenital myopathy
     a. Arthrogryposis multiplex
  4. Myositis ossificans
  5. Myoglobinuric myopathy

Nonhereditary myopathies
- A. Dermatomyositis
- B. Polymyositis
- C. Nonspecific myopathies
- D. Myopathy and polymyositis associated with systemic disease
  1. "Collagen disease"
     a. Scleroderma
     b. Lupus erythematosus
     c. Periarteritis nodosa
     d. Rheumatoid arthritis
  2. Carcinomatous myopathy
  3. Endocrine disorders
     a. Thyroid
     b. Adrenal
     c. Parathyroid
  4. Other metabolic disorders
     a. Abnormality of glycogen breakdown (McArdle)
     b. Glycogen storage disease
     c. Primary amyloidosis
  5. Sarcoidosis
  6. Infection
     a. Trichinosis
     b. Others
- E. Myasthenic myopathy and myasthenic polymyositis

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*Major Categories: The Muscular Dystrophies.—*

*Classification and general features:* The separation of wasting diseases of muscle into the "atrophies" and "dystrophies" occurred at the close of the nineteenth century. Concomitantly, it was found that many cases of muscular dystrophy occurred in families, and that while the distribution of weakness might be constant within a given family, there were variations between families. As these variations were described, a host of eponyms was introduced.

The problem of classification has been re-examined by several authors within the last decade, based on the study of large groups of cases in several parts of the world.[3,25,39,40,47,49] Although the basis for classification has differed somewhat in these various reports, that used by Walton and Nattrass[49] seems reasonable at present. The essential features are listed in Table II.

The major advantage of this classification is one of prognosis, but it also implies a distinct difference between the two most clearly defined categories, the Duchenne and facioscapulohumeral types. The major drawback of the scheme is that the category of limb-girdle dystrophy is apt to be a wastebasket, including not only a variety of clearly defined familial syndromes, but also sporadic cases which are more vague in their outlines. Furthermore, transitional and borderline cases are not infrequently encountered.

TABLE II. PROGRESSIVE MUSCULAR DYSTROPHIES

| | DUCHENNE | FACIOSCAPULOHUMERAL | LIMB-GIRDLE |
|---|---|---|---|
| Age at onset | Childhood | Adolescence | Early or late |
| Sex | Male | Either | Either |
| Pseudohypertrophy | Common | Rare | Uncommon |
| Initial distribution | Pelvic girdle | Shoulder girdle | Either |
| Involvement of face | Rare | Always | Never (?) |
| Rate of progression | Relatively rapid | Slow (abortive) | Intermediate |
| Contractures and deformity | Common | Rare | Occasional |
| Inheritance | Sex-linked recessive | Dominant | Either |

Several features are common to all three groups: Affection of the muscles is initially proximal in distribution and although it may ultimately become global, proximal muscles are still more severely affected. Except for the face, cranial musculature is spared. Deep reflexes are depressed. Fasciculation is only rarely seen. Remission and recovery do not occur, although mild and arrested cases may be encountered. Pathologic changes in the muscles are similar and consist of alterations of muscle fibers with varying degrees of fat deposition and connective tissue proliferation. Leukocytic infiltration of muscles is rare, and the intramuscular nerve endings are normal. Evidence of regenerative activity is usually lacking, and the growth pattern of dystrophic muscle in tissue culture is abnormal, but there is a normal histologic response to experimental injury. Electromyographic abnormalities are similar. Although the pattern of inheritance varies from group to group, the clinical features within a single family are usually constant.

DUCHENNE TYPE MUSCULAR DYSTROPHY: The eponym has been retained for this variety because it is not possible to provide a precise descriptive term. Most cases begin before the age of 3 years, but onset may be delayed until adult life, so "childhood muscular dystrophy"[39] is not adequate. "Pseudohypertrophic muscular dystrophy" is not entirely satisfactory because, even though enlargement of the muscles occurs in most cases, it may be lacking in some and may occasionally be found in other varieties. The decision as to whether pseudohypertrophy is actually present depends upon the imperfect subjective impression of the examiner. Stevenson[40] included the words "young boys" in his title for this category and insisted that it does not occur in girls. Occasional clinically similar cases in girls have been reported, although they have usually started later in childhood.

Symptoms are usually first noted when the child begins to walk. Frequent falls, waddling gait, toe-walking, and difficulty in climbing are common modes of onset. Involvement of the arms occurs later, and predilection for the sternal portion of the pectoralis major, the lower protion of the trapezius, and upper portion of the deltoid is striking. The face is characteristically unaffected. The typical mode of rising from a supine position (Gowers' sign) is due to pelvic girdle and trunk weakness. It is frequently found in these children, but is not pathognomonic because it also occurs in other conditions which cause weakness in this distribution.

"Pseudohypertrophy" is attributed to deposition of fat and most often affects the gastrocnemius. Other frequent sites are the triceps, infraspinatus, and vastus lateralis. There is relatively rapid progression, leading to contractures, deformity, disability, and early death, usually in the second or third decade.

The pattern of inheritance is sex-linked recessive. The large number of sporadic cases is accounted for by a high mutation rate and occurrence in girls is attributed to occasional autosomal recessive inheritance.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY: This variety may occur in either males or females. Onset may occur at any time, although usually after adolescence. Progression is slow and the disease is compatible with longevity; although disability may be considerable in some cases, abortive forms are not infrequent. Mildly affected persons may not be recognized as such by their relatives so that in genetic studies, it has been necessary to examine all relatives of probands. The pattern of inheritance is usually autosomal dominant,[39,47,49] but in Northern Ireland was recessive.[40]

Weakness usually starts in the shoulder girdle, with very slow progression to involve muscles of the pelvic girdle. The face is regularly involved; in a few families, affection of the face may be delayed or absent in some individuals but is present in others. Because these patients are usually ambulatory for a longer period of time, exaggerated lordosis and pronounced winging of the scapulae is more prominent than in the Duchenne variety. Pseudohypertrophy rarely occurs.

LIMB-GIRDLE MUSCULAR DYSTROPHY: The features of this category are intermediate for each of the criteria by which the others are distinguished. It may occur in either sex, inheritance is usually recessive,[47,49] but may be dominant,

either the shoulder or pelvic girdle may be involved first, and the rate of progression is variable. Pseudohypertrophy is rare, and so are contractures. This classification includes the scapulohumeral juvenile variety of Erb, the atrophic pelvifemoral type (Leyden-Moebius) as well as familial instances of "muscular dystrophy of late life." Variation in distribution of weakness and tempo of progression in sporadic cases make it likely that there will be ultimate subdivision of this category when more fundamental knowledge is available.

*Visceral involvement:* Lesions of the myocardium similar to those in skeletal muscle have been described by Nothacker and Netsky,[32] who summarize earlier reports. Clinically significant heart disease is unusual, although several instances of congestive heart failure have been recorded. Abnormalities of the electrocardiogram are not infrequent, but there is no consistent pattern; short PR interval, abnormal Q waves, high voltage QRS complexes, and other changes have been noted. Ballistocardiographic patterns are also abnormal in high percentage. On the basis of cardiac catheterization studies, it has been suggested that the sedentary life to patients with advanced disease is protection against incipient heart failure.

Abnormalities of gastrointestinal smooth muscle have been reported in some autopsied cases, but these were asymptomatic. Rare instances of muscular dystrophy in association with disease of the central nervous system or other organs have occurred,[3] but there is no evidence that these coincidences have significant implications relating to pathogenesis of the usual case.

*Metabolic studies:* The general features of these disorders and the fact that they are often inherited have suggested that the muscular dystrophies are fundamentally disorders of metabolism. If so, there is no reliable clue as to the nature of the metabolic defect; it is only conjectured that the defect is actually in muscle. It is possible that muscle is only the target of a more generalized abnormality, similar to the spinal cord in combined system disease accompanying pernicious anemia.

PROTEIN: Although wasting of muscular tissue is an outstanding feature, balance studies for one week showed no negative nitrogen balance, so that the process must be very slow. Decreased concentrations of "noncollagen nitrogen," myosin, myoglobin, and a variety of other cellular constituents have been observed which could be the result of any wasting process.

There is little information regarding the contractile proteins. In preliminary studies, myosin from dystrophic muscle has been different from normal in birefringence and electrophoretic mobility. In a study using fluorescent antibodies of normal human myosin, even advanced dystrophic muscle picked up the label.

There is no consistent abnormality of serum proteins, either in total amount or electrophoretic analysis. Low values of serum gamma globulin were found in one study of myotonic dystrophy which did not seem to be the result of impaired production because the response to antigenic challenge was normal.

Aminoaciduria was first reported in 1948, and has subsequently been confirmed by several other workers. There is no consistent or specific pattern of amino acid excretion. Aminoaciduria has been found in asymptomatic siblings of patients, it is not always present in dermatomyositis, and may be inherited

independently of the myopathy in myotonic muscular dystrophy, so that it may not be due merely to "leakage" from diseased muscle.

ENZYMES: In a series of publications, Dreyfus, Demos, and the Schapiras[13,14] reported increased serum levels and decreased muscle levels of aldolase, lactic dehydrogenase, phosphohexosisomerase and transaminase. These findings have been confirmed by several other reports. Serum enzyme levels are most consistently elevated in the Duchenne variety in childhood. Among adult survivors, enzyme activity is apt to be normal, so that measurement may have some use as an index of activity of the disease. The significance of abnormal enzyme activity is not clear; if it reflects a change in membrane permeability with consequent leakage of high molecular weight proteins from muscle to blood, there must also be a change in the rate of synthesis of these enzymes to maintain an elevated blood level over a protracted period.

In contrast, the French workers found no decrease in concentration of the cytochromes in muscle, and alkaline phosphatase has been reported to be normal in muscle and serum.

CREATINURIA: Increased urinary excretion of creatine and diminished excretion of creatinine have long been recognized as features of muscular dystrophy, although occurring in other wasting conditions as well. The rate of creatine formation in the liver has been shown to be normal in dystrophy. Benedict and associates[5] followed the concentration of isotopic nitrogen in urinary creatine and creatinine after the administration of labelled glycine. Since urinary creatinine is derived solely from muscle creatine, urinary isotope concentrations should be the same in both compounds if the creatine were also derived from muscle. They actually found that the abundance of $N^{15}$ in urinary creatine was initially much higher than in creatinine and declined more slowly. They interpreted this to mean that the urinary creatine had never actually been part of the muscle pool. However, isotope concentration in urinary creatinine was actually higher than normal controls, suggesting that whatever muscle survived was competent to convert creatine into creatinine. They concluded that creatine formation is normal in muscular dystrophy, but because of the diminution in functional muscle mass, conversion of creatine to creatinine is diminished.

Other data suggest that creatinuria may not be merely the result of diminished muscle bulk. In some conditions (amyotrophic lateral sclerosis, myotonic muscular dystrophy) muscle wasting of considerable degree may be associated with only mild creatinuria and in other conditions (polymyositis, thyrotoxicosis) creatinuria may occur without much muscle wasting. (The degree of creatinuria has not actually been correlated with measurements of lean body mass.) There have also been occasional reports of diminished creatinuria without change in clinical status after the administration of a variety of compounds. Furthermore, muscle concentrations of creatine, creatine phosphate, and creatine kinase are all reported to be low.

It has been suggested that the diminution in urinary creatinine excretion is a more reliable index of myopathy than the increased excretion of creatine. Simultaneous measurement of lean body mass and creatinine excretion have shown a good correlation, not only in muscular dystrophy but also in other wasting conditions.

*Carbohydrate metabolism:* Abnormalities in glucose tolerance have been reported occasionally but were not found in three recent careful studies. Pyruvate values after a glucose load have been normal, and although the fall in serum phosphate was less than normal in two studies, this finding was not confirmed in a third. Differences in response of blood sugar to exogenous insulin and epinephrine have been attributed to diminished muscle mass.

The occurrence of ribosuria in muscular dystrophy was reported in 1949, and it has recently been suggested that as residual muscle mass is reduced, there is significant excretion of ribose. Several other reports have failed to confirm this, however.

*Inorganic elements:* Studies with isotopic potassium have indicated that there is a reduction of the concentration of potassium relative to "fiber water" and in total body "exchangeable potassium." This has been attributed to loss of tissue rather than to an alteration in rate of turnover in surviving muscle, but apparently healthy siblings may also have diminished exchangeable potassium. No abnormalities of serum calcium and phosphorus have been found, and balance studies of phosphorus and magnesium have been normal. "Bone atrophy" has been reported, but roentgenographic abnormalities can be accounted for on the basis of immobilization, disuse, and abnormal postures.

*Endocrine function:* In contrast to myotonic dystrophy (*v.i.*), there is no endocrinopathy in the progressive muscular dystrophies. Basal metabolic rates, while occasionally low, are rarely abnormal and show no consistent trend from normal. Serum protein-bound iodine is within normal limits, and disposal of exogenous thyroxin is normal. Urinary excretion of pituitary gonadotrophins and 17-ketosteroids is normal, and treatment with a variety of pituitary, adrenal, and gonadal hormones has been ineffective.

*Vitamin E:* Because of the histologic similarity between some forms of myopathy in animals due to experimental vitamin E deficiency and human muscular dystrophy, considerable attention has been devoted to study of this vitamin. However, there are significant differences between the two conditions histologically and biochemically. The most important difference is that the animal myopathy responds to replacement therapy with vitamin E while the human disease is unaffected by the vitamin or its metabolites. No defect of absorbtion has been demonstrated, and both serum and tissue levels of tocopherol are normal in human muscular dystrophy. In infants with definite tocopherol deficiency, creatinuria occurs and is diminished by replacement therapy and in one case of tocopherol deficiency due to cystic fibrosis of the pancreas, there were necrotic lesions of muscle but not the clinical picture of muscular dystrophy.

*Therapy:* Innumerable remedies have been proposed and found valueless[29]; there is, unfortunately, no therapeutic agent at present. The most recent fad in the United States was the administration of protein hydrolysates and vitamins, but this, too, failed when tested critically in several centers. Physical therapy may be of value in the prevention of deformity, in maximizing use of residual muscle and providing mechanical aids for the acts of daily life, but in the long run, it is of limited value in progressive cases. Surgical correction of deformities may sometimes be of value, but the period of immobilization required by exten-

sive procedures may itself be deleterious. Periods of bed rest for any reason may be followed by deterioration of muscle function. The psychologic requirements of children with a severely disabling chronic illness pose many problems.

## MYOTONIC SYNDROMES

*Myotonic Muscular Dystrophy.—*

*Myopathy:* The weakness and wasting of myotonic muscular dystrophy differ from that of the progressive muscular dystrophies primarily in the distribution of affected muscles. Rather than involving the more proximal parts of the extremities, it usually starts distally. Involvement of the hands and feet usually precedes weakness of shoulder and pelvic girdles. There is also a special predilection for muscles of the neck; the sternocleidomastoid muscles are characteristically reduced to thin ribbons. Cranial muscles, especially the temporals and masseters, are usually affected. These muscles may be markedly atrophic before they are symptomatically weak. The hollowing of the temporal fossae and sunken cheeks, when combined with frontal baldness and ptosis of the eyelids, produces a characteristic facial appearance. Oropharyngeal muscles are not infrequently affected, and dysarthria may occur. Weakness of ocular movements may also be present. When the disease is far advanced, weakness and wasting may be generalized, but the characteristic features are still discernible.

Although myotonic dystrophy may make its appearance in childhood, it usually begins in young adults of either sex and symptoms may appear for the first time in middle age. The course of the disease shows considerable variation; a few patients are seriously disabled, while others go for many years with only minor difficulty. Stigmata of the disorder may be present in asymptomatic individuals. The pathologic changes are similar to those of the other dystrophies[1,19] except that sarcoplasmic masses, centrally placed nuclei and ringed fibers are more common.

*Myotonia:* This phenomenon is characterized by abnormally slow relaxation of a muscle after contraction. "Peripheral" or "reactive" myotonia may be elicited by electrical or mechanical stimulation. "Active" myotonia describes the slow relaxation after a volitional contraction. Usually the myotonia becomes less marked with succeeding contractions, but occasionally the reverse may be true ("myotonia paradoxica"). Electromyographically, myotonia is accounted for by repetitive discharge of single muscle fibers at high frequency. As the units cease firing, a gradual disappearance of potentials is seen in optical records and, in audio amplification, the sound gradually fades away, giving a characteristic "dive-bomber" effect.

Difficulty in releasing grasp may be noted for many years before the onset of weakness. On the other hand, weakness may precede myotonia, and in some otherwise typical cases, myotonia may be entirely absent.

Mechanical myotonia may be elicited from the muscles of the thenar eminence or tongue, but not usually from other muscles, while electric stimulation may evoke the myotonic response from a wider area. In rare cases, the myotonia has been demonstrated to involve respiratory muscles, causing a syndrome of hypoventilation.

Considerable study has been directed to the nature of myotonia. A similar phenomenon occurs as an hereditary condition of goats and the peripheral nature of myotonia in these animals was demonstrated by its persistence after nerve-section or curarization. Analagous experiments were subsequently done in humans, in whom myotonia persists after spinal anesthesia, nerve block, and intra-arterial administration of curare, but is abolished by the intramuscular administration of procaine and diminished by intramuscular calcium. These studies indicate that the myotonia is a property of the muscle fiber independent of the motor neurone, nerve, or neuromuscular junction.

Increased sensitivity to acetylcholine, neostigmine, and potassium chloride have been reported, but the response to neostigmine has been variable. Quinine and procaine amide have reduced the myotonia. Adrenocorticotrophic hormone (ACTH) and cortisone have been found to reduce myotonia by some authors but not by others, and the response to a variety of other pharmacologic agents has been inconstant, so that no coherent theory has been possible. Because of the apparent antagonism of neostigmine and quinine, there were several studies of serum and muscle cholinesterase, which proved to be inconclusive.

The consensus at present is that all of the observed phenomena may be accounted for by an hyperexcitable state of the muscle membrane.[24]

*Cataract:* The incidence of cataract in myotonic dystrophy differs in various reports; Walsh[45] states that upon slit lamp examination, some evidence of cataract formation is seen in "almost all" cases, but there have been advanced cases in whom no opacity was detectable. In slit lamp examination, multicolored small dots are seen just beneath the anterior and posterior capsules. Opthalmoscopically a star-shaped opacity may sometimes be seen at the posterior cortex. As the cataract matures, it may become indistinguishable from other forms. In some families, the presence of cataract may be the only taint of the disease in relatives of others who show all the manifestations.

*Inheritance:* Several detailed studies of the pattern of inheritance have indicated a Mendelian dominant pattern, although Walton and Nattrass suggest that in some families a combination of recessive genes might be responsible. It is not clear whether one gene or several is responsible for the entire constellation. In some families, the phenomenon of "anticipation" (appearance at an earlier age in succeeding generations) and "potentiation" (appearance of more features and more severe forms in succeeding generations) have been noted. Thus, cataracts only may be present in one generation, while the next will have mild myopathy and the third a severe form. The early appearance of gonadal insufficiency may obliterate the disease in a family.

*Endocrinopathy:* The most consistent abnormality of endocrine function in patients with myotonic dystrophy is gonadal insufficiency. Testicular atrophy was present in 37 of the 43 men in Thomasen's series.[42] This may even underestimate the actual frequency because histologic changes have occurred in almost all cases examined at autopsy or by testicular biopsy. Hyalinization of the tubles is the most constant alteration; the Leydig cells may be normal or increased. Although deviations have been noted, the histologic picture is often similar to that described as Klinefelter's syndrome. Urinary excretion of pituitary follicle stimulating hormone has been measured in 23 cases, and in 10, the values were

elevated. It is therefore concluded that the gonadal insufficiency is not secondary to pituitary failure, although minor changes are occasionally found in this gland at autopsy. The onset of hypogonadism probably occurs after puberty since skeletal proportions, development of the penis, secondary sex hair, and voice are all normal. Menstrual irregulatities and sterility are common in women with the syndrome, but ovarian failure is less frequent or overt than the testicular disorder.

The basal metabolic rate is usually in the low normal range and not infrequently is abnormally low.[42] Some reports state that the incidence of colloid goiter is high. However, frank clinical evidence of myxedema is very rare; radioiodine uptake and turnover, serum protein-bound iodine, and response to thryoid-stimulating hormone have almost always been normal, although at least one case with well-documented associated hypothyroidism is on record. It has been postulated that the low metabolic rate is due to loss of muscle mass, but similar metabolic depression is less common in other wasting conditions. Furthermore, creatinuria, also attributed to loss of muscle mass, is less marked in myotonic dystrophy than other forms. If both creatinuria and lowered metabolic rate are to be attributed to the same cause, the changes should be parallel, but they are not. We have recently seen a patient with myotonic dystrophy whose metabolic rate was minus 30 per cent (radioiodine uptake and serum protein-bound iodine normal), but there was no abnormal creatinuria (30 mg. per day). If there is actually a consistent trend to lowered metabolism in myotonic dystrophy, the cause is not known.

Abnormalities of adrenal function have been suggested by diminished urinary excretion of 17-ketosteroids which is usually found in both sexes, and in some cases by abnormal responses to epinephrine, insulin, and water-loading. However, these tests are nonspecific; more direct measurement like the response to ACTH of urinary 17-ketosteroids or serum corticoids has been normal in most of the cases reported. No case of frank Addisonian adrenal insufficiency has been recorded.

Diabetes occurs in patients with mytonic dystrophy, but there is no indication that the frequency differs from that which might occur by chance.

*Visceral involvement:* Fisch[16] collected 85 cases from the literature and found that the electrocardiogram was abnormal in 68 per cent. Of these, 48 per cent had abnormalities of conduction (prolonged P-R intervals or abnormal QRS complexes). Clinically significant abnormality of rhythm has been unusual, but there have been a few cases of congestive heart failure and in several cases, the myocardial changes at autopsy have resembled those in skeletal muscle. There is no good evidence that smooth muscle of the gastrointestinal tract is significantly affected, although functional esophageal abnormalities have been observed. The significance of a recently reported abnormality in composition of gastric juice in myotonic dystrophy is uncertain, and isolated reports of sprue in myotonic patients are probably coincidental. No consistent lesions of the central or peripheral nervous systems have been found, and although the incidence of mental deficiency has been reported to be high in some series, this has not been true in others.

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*Myotonia congenita and paramyotonia congenita:* The myotonia of myotonia congenita is the same as that in myotonic dystrophy in its electrical and pharmacologic characteristics. It differs, however, in that it is more likely to be the symptom for which the patient seeks aid; muscular weakness is not a feature of the congenital disorder. The myotonia also differs in its wider distribution; percussion myotonia may often be demonstrated in any muscle. Symptomatically, difficulty in initiating movements and stiffness have most often affected the legs, but the hands and, in some cases, even ocular movements, have been involved. Another difference in the myotonia is its earlier onset, which is usually in childhood and may appear in infancy. Impressively large muscles may be seen.

The other features which characterize myotonic muscular dystrophy are lacking in myotonia congenita; weakness and wasting, cataract, endocrinopathy, and cardiopathy are all absent. Furthermore, the clinical features of one condition do not usually appear in isolated members of a family affected by the other. On the basis of these differences, most writers separate the two categories, but transitional cases have been reported. Maas and Paterson[26] and others have insisted that there is a basic identity between the two conditions.

In about a third of the cases, myotonia congenita is inherited; the pattern in these families is usually dominant.

Most patients with myotonia experience increased stiffness in cold weather, but there is a syndrome in which myotonia, especially of the orbicularis oculi, is characteristically brought out only by cold (paramyotonia). This, too, may be inherited in dominant fashion. This rare condition has been reviewed by Drager, Hammill, and Shy[12] who note that percussion myotonia is frequently limited to the tongue. Paramyotonia also differs from the other two myotonic syndromes in the frequency of attacks of flaccid paralysis, which are precipitated by cold and during which myotonia is abolished.

The possibility that myotonia may occur after polyneuritis or systemic infections is debated. This kind of "myotonia acquisita" may often occur in patients whose relatives show evidence of either myotonic dystrophy or myotonia congenita, implying that the "acquired" myotonia was really present previously, but not recognized. Electromyographic abnormalities similar to the myotonia of these conditions have been reported in Duchenne type dystrophy, polymyositis, and a variety of other conditions, but these have not been associated with clinical evidence of myotonia.

*Treatment:* When myotonia is troublesome, quinine (0.3 to 0.6 Gm. several times daily) is usually of some value. Effective doses of quinine may cause unpleasant side effects, and Thomasen has found that a once effective level may become ineffective after a while. As an alternative, oral administration of procaine amide (4 to 6 Gm. daily) has been found to be of value. Because of unpredictable effects and potential hazards, trials of cortisone and ACTH are probably best reserved for more refractory cases. It is actually only rarely necessary that the myotonia be treated; in myotonic dystrophy, weakness is usually much more troublesome than myotonia, and in myotonia congenita, affected persons are usually able to "work off" the stiffness before proceeding

with activity. Thomasen describes myotonic brothers who were able to be effective circus acrobats after "warming up."

There is no specific treatment for the weakness of myotonic dystrophy. The cataracts may be treated surgically according to ophthalmologic indications, and there is rarely need for endocrine replacement therapy. Androgenic hormones and thyroid extract do not affect the myopathy.

### OTHER FAMILIAL MYOPATHIES

*Distal Myopathy.*—Gowers described cases in which myopathic wasting was primarily distal in distribution, unlike the classical varieties. Since then, there have been a number of isolated reports of similar cases. Differentiation has to be made from peroneal muscular atrophy, and some of the reported cases may have been instances of myotonic muscular dystrophy in which myotonia was lacking. Welander,[50] in a monograph describing detailed studies of 249 patients, has established the myopathic nature of this disorder. Characteristically, weakness and wasting start in the upper extremities and progress very slowly to involve the legs; cranial muscles are rarely affected. Deep reflexes are depressed, but there are no fasciculations, myotonic phenomena, or sensory loss, and the electromyographic and biopsy patterns are those of myopathy. In 3 patients examined at autopsy, there were no lesions of the central or peripheral nervous system. The disorder usually starts in adult life and only rarely causes severe disability. Inheritance is usually dominant.

*Ocular Myopathy.*—Involvement of ocular muscles in the usual varieties of muscular dystrophy is extremely rare, except for myotonic muscular dystrophy. Kiloh and Nevin,[23] however, have described a series of cases of ptosis and ophthalmoplegia in which biopsy and electromyography of the affected muscles have indicated primary pathology in the muscles. They pointed out that cases previously reported as "progressive nuclear ophthalmoplegia" were probably also in this category in that the reports of autopsy examinations were inadequate to establish the primacy of nuclear pathology. Subsequent neuropathologic examination of similar cases[4] has confirmed the conclusions of Kiloh and Nevin. The disorder usually starts in early adult life and is slowly progressive; diplopia may be absent because of symmetrical involvement. Fluctuations in the degree of ptosis have been observed, but major remissions are lacking, and when tested with neostigmine, no response has been obtained. Involvement of other muscles has occurred in many cases, in patterns suggesting a relationship to either facioscapulohumeral or myotonic muscular dystrophy; it is possible that some were actually instances of these dystrophies. About half of the cases have had a family history of similar disorder, and most often the pattern of inheritance has been dominant. In some sporadic cases, a relationship to myasthenia gravis is suggested.[36]

*Congenital Myopathy.*—Among infants with flaccid weakness and hypotonia, the majority have progressive disease and die of infantile progressive spinal muscular atrophy (Werdnig-Hoffman syndrome).[6,46] Among survivors, many specific disorders have been identified in a small percentage of cases. There is

one group in whom improvement occurs and may be complete, for whom the term "amyotonia congenita" may be reserved, although this title has fallen into disrepute. A certain proportion do not recover completely but are left with minor degrees of weakness and underdevelopment of muscles. Affection of the muscles has been more marked proximally in some cases,[38,43] but not all.[46] Some of these cases have occurred in families,[38,43] and show histologic evidence of myopathy. Some cases of arthrogryposis multiplex congenita are also attributed to congenital myopathy.[2]

*Myositis ossificans:* This unusual and dramatic condition is often familial, has been reported in twins, and is frequently associated with congenital anomalies (especially microdactyly of the thumbs and great toes) which may also occur in otherwise unaffected relatives. Onset of the disease is before the age of 5 years in more than half the cases. Solitary or multiple soft-tissue masses, often painful, appear on the dorsum of the neck or back and may ulcerate. There follows a period of fibrosis of these lesions, and ultimately the deposition of calcium and ossification. In early stages, muscle fibers in the involved areas show varying degrees of dissolution, and they are ultimately replaced by connective tissue and bone. There has been difference of opinion as to whether the muscle is involved primarily and the connective tissue response is secondary, or the reverse. As more of these lesions appear, progressive development of ankyloses occurs and complete immobilization results. Local trauma, including biopsy of lesions, may be followed by exacerbations. The etiology is unknown, and there is no specific therapy, although ACTH and cortisone have been reported to be beneficial in a few cases.

*Myoglobinuric myopathy (paralytic paroxysmal myoglobinuria, Meyer-Betz syndrome):* Although there are only 36 cases of this condition in the literature at the present time, it is clear from the increasing number of reports in recent years (15 cases reported since 1953) that paroxysmal myoglobinuria is probably not so rare. Two-thirds of the cases have occurred in men. The occurrence of more than one case in a family has been recorded twice definitely and possibly in two others. Some patients died in the first attack, while others have had as many as fifty episodes over a period of 37 years. Pain in the back and extremities is followed by weakness which may be mild or profound; respiratory or bulbar paralysis caused death in a few cases. The appearance of a dark red or brown pigment in the urine is usually delayed until 12-24 hours after the onset of an attack, but in one experimentally induced attack, the interval was only 90 minutes. Pigmenturia usually lasts 24 to 48 hours, but recovery of strength is more prolonged. The major threat to life is anuria and renal failure which caused death in 8 cases. Attacks in 2 susceptible persons were induced for experimental study and were followed by anuria, fortunately not fatal. Precipitating factors have included exertion (which has varied from simply crouching to heavy work), respiratory and other infections, and surgery. Some of these features are illustrated by the following case, which is unique as far as an apparent relation to the menses is concerned.

L. J., a 36-year-old woman, had seven episodes in a period of 8 months; 5 of the attacks coincided with the onset of menses; the others were associated with respiratory infections. The

attacks started with pain and swelling of the arms and legs. Within a day or so, walking was impossible, and she required assistance in dressing and eating. Motion was restricted by both pain and weakness, and she would remain in bed with her arms folded on her chest. Dark urine was usually noticed on the second day and lasted for 2 or 3 days. Pain abated in 3 or 4 days, but weakness usually persisted in varying degrees for a week or so. She was seen on the third day of the last attack.

Her temperature was 100.6° F. She looked acutely uncomfortable, and there was tenderness over the kidneys, but general examination was otherwise unremarkable. The cranial muscles were all normal, but there was weakness of the neck and extremities against resistance. She could walk, but only on her toes; attempts to lower the heels caused pain in the calf. She was unable to extend her knees or elbows completely. The muscles were not notably tender, but pain was referred to the fixing joint when motion was attempted. Reflexes were normal except that the Achilles reflexes were absent.

There was no anemia or leukocytosis, and the serum appeared normal. The urine was dark brown, gave a strongly positive test for albumen, and contained 10 white blood cells per high power field, but no red cells. The guaiac test on the urine was positive, but there was no porphobilinogen. The urinary pigment was identified spectroscopically as myoglobin. No abnormal hemolytic tendency was detected, and the red cells did not sickle, but the Mazzini and treponema immobilization tests were positive. Serum levels of lactic dehydrogenase, phophohexoseisomerase and glutamic-oxaloacetic transaminase were elevated to values of 2,950, 1,580, and 1,500 units, respectively, compared to normal levels of 600, 40, and 40 units. Enzyme activity was also found in the urine (P.H.I. 56 units, G.O.T. 23 units, on the second day). By the ninth hospital day, serum enzyme activity had fallen to normal levels. Chronaxie studies showed elevated figures, but less than observed in denervation. Unusually rapid interference patterns and positive potentials but no fibrillation were seen in electromyographic studies. A muscle biopsy taken on the day after admission showed numerous fibers manifesting changes of coagulative necrosis scattered among others which appeared normal. In many of these fibers, the cytoplasm appeared basophilic. There was no leukocytic response.

Her course was one of progressive improvement. The urine cleared within 48 hours after admission, pain subsided in a few days, but at the time of discharge 2 weeks later, she still had diffuse weakness of the arms against resistance and proximal weakness in the legs. The Achilles reflexes were still absent.

The relationship of this syndrome to other myopathies is not clear. Seven patients have had persistent weakness and wasting, but it is not known whether this causes or results from the paroxysmal attacks. Three patients had relatives affected by myopathy without pigmenturia. Four others have had weakness of longer duration resembling polymyositis but complicated by pigmenturia. In most cases, there was severe coagulative necrosis of muscle fibers with no inflammatory reaction; sometimes, muscle biopsies were normal.

The etiology is unknown. No definite abnormality of myoglobin was demonstrated in the two cases studied, and the heart has not been involved in any case. It is possible that myoglobin is only one of many muscle constituents released during an attack. Creatinuria and aminoaciduria are also paroxysmal in these patients, and the marked transient elevation of serum enzymes in our case was also found in the case of Pearson, Beck, and Blahd.[33] The positive serologic test for syphilis in the present case probably has no connection with the muscle disease; it has not been found in other cases.

There is no specific treatment. ACTH did not prevent the development of an attack in one case and alkalinization of the urine does not guarantee against the danger of renal failure.

NONHEREDITARY MYOPATHIES

*Dermatomyositis.*—After the original descriptions, in 1903, Steiner defined dermatomyositis as an "acute, subacute or chronic disease of unknown origin characterized by edema, dermatitis and multiple muscle inflammation." This definition has not changed significantly in the intervening years. There have been recent monographs by Talbott and Ferrandis,[41] Garcin and associates,[17] and Walton and Adams.[48]

Among 573 cases collected from the literature, Schuerrman[37] found 55 per cent in women. Age at onset varied from 1½ to 74 years, with roughly equal distribution in all decades from the first to sixth. Rare cases have been described in sisters and twins. No racial or geographic peculiarities are known, but there has been no epidemiologic study.

*Clinical Features.*—

*Skin:* The characteristic dermatitis is manifested by edema and erythema, with a pink, "heliotrope" hue, involving the face and upper trunk. There is special predilection for the periorbital areas; edema and erythema of the eyelids may be the sole manifestation of cutaneous involvement. Malar erythema may resemble the rash of lupus erythematosus. The hands are frequently involved, especially the extensor surfaces and nail beds. Rash on face or hands as the presenting symptom occurred in over half the cases of one series and appears ultimately in most cases. Pigmentation and lividity of the extremities and hardness of the skin resembling scleroderma may occur; alopecia is an inconstant feature. Many other varieties of dermatitis have been described, and there are no pathognomonic histologic changes in the skin.

Calcinosis is a common consequence among survivors. It occurred in one-third of children in several reports, but in only 5.5 per cent of patients older than 16 years in the large series of Christianson, Brunsting, and Perry.[9]

*Muscle:* Pathologic alteration of muscle fibers attended by variable infiltration of mononuclear cells is characteristic. The leukocytic infiltration may be mild or extensive. There is usually evidence of regenerative activity. The clinical expression of this is weakness, which may precede or follow the dermatitis by weeks or many months. Weakness is almost always proximal in location, affecting both shoulder and pelvic girdles. In severe cases, weakness may be global, and respiratory paralysis may lead to a fatal outcome. Facial and masticatory muscles are involved in a minority of cases, but dysphagia has been reported in more than half of the patients in each of the large series. Palatal weakness, resulting in dysarthria and nasal regurgitation, may imply a serious prognosis.

Ptosis occurs on occasion, but ocular muscles are only rarely affected. One case with complete ophthalmoplegia is described in detail[34] and another is mentioned.[17] Two other cases with partial ophthalmoplegia have been reported but were atypical in other respects, and although diplopia is occasionally mentioned as a symptom, details of examination are lacking.

The muscles are often painful and tender but are not in perhaps an equal number of patients, and this cannot be a crucial diagnostic point. Deep reflexes may be present early in the course, but tend to be diminished and, ultimately,

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absent. Electromyography is characterized by evidence of increased irritability, including fibrillaiton potentials and "pseudomyotonic" discharges, which occurs only rarely in the dystrophies.

*Systemic involvement:* Fever, splenomegaly, weight loss, Raynaud's phenomenon, light sensitivity, and arthralgia are inconstantly seen. Myocarditis is not infrequently seen at autopsy and may cause heart failure. Serositis is rare, and although ulcerations and bleeding of the gastrointestinal tract occur, this may be an indirect effect of the disease or steroid therapy. Interstitial pneumonitis and renal or hepatic failure are distinctly rare. Retinal exudaets have been reported in a few cases. The general lack of visceral involvement is one of the features which distinguishes dermatomyositis from lupus erythematosus and scleroderma.

Peripheral neuritis is reported to occur ("neuromyositis"), but the evidence is inconclusive and this must be rare, if it happens at all. Electromyographic abnormalities have been interpreted as indicative of involvement of terminal nerve endings but could be due to abnormalities of muscle alone. Cases reported with involvement of the central nervous system are so atypical that this may be considered "virtually unknown."[48]

*Laboratory data:* Anemia, leukocytosis, eosinophilia, and elevation of the erythrocyte sedimentation rate are inconstant features. Elevation of serum gamma globulin has been recorded. Creatinuria is frequently present but may be lacking. Elevation of serum enzymes may subside concomitantly with clinical improvement, but values may be normal in apparently active cases.

*Course:* Although there is some variation in different series, over half the cases have been fatal. Schuerrmann found a somewhat more serious prognosis in older age groups. It is stated that if the patient survives the first year, prognosis for life is good. Of the survivors, about 10 per cent recover completely, and the remainder are incapacited in varying degree by weakness, atrophy, and contractures. Although the process tends to remain stationary once quiescence has occurred, there been several instances of remission and relapse.

*Therapy:* Therapeutic success has been claimed for many drugs, but variability and unpredictability of the course render evaluation of therapeutic measures difficult. ACTH and cortisone or its derivatives are the most popular agents today, and there have been many instances in which a direct beneficial action of these compounds is suggested. Christianson and associates state that they have seemed life-saving on occasion. Therapeutic response has occurred in both acute and chronic cases, and even disappearance of calcinosis was reported in one case. Maximum dosage should be used; Talbott and Ferrandis[41] suggest increasing dosage until there is a therapeutic effect or a Cushing OID syndrome results. The complications of steroid therapy may occasionally force abandonment of this approach. It should be noted that there has been no well-controlled study of the therapeutic effects of steroids, and according to Schuerrmann, the advent of these agents has had no detectable effect on the over-all mortality.

Because of the possibility of eventual recovery, every effort should be made to avoid the development of contractures and to maintain muscle function by physical therapy.

*Etiology:* The pathogenesis is not known. The inflammatory reaction in muscles suggests the possibility of infection, but no organism has been demonstrated, and the use of antibiotics (except to control secondary infection) has been largely abandoned. Coxsackie virus was isolated from the stool of one patient, but subsequent efforts to confirm this have been fruitless.

The relationship of dermatomyositis to lupus erythematosus and scleroderma, the appearance of the syndrome after infections and drug reactions, the similarity of lesions to those produced in rabbits by a muscle antiserum, and the occasional elevation of serum gamma globulin or antistreptolysin titer have led some to suggest a hypersensitivity reaction.

Considerable attention has been given to the frequent association of dermatomyositis with malignant disease. There are at least 117 instances in which the site of malignancy is recorded (Table III); the site of the tumor varies. Dermatomyositis occurs only rarely among patients with carcinoma, but there were 41 cases of malignancy among 382 patients with dermatomyositis (10.7 per cent) in the combined figures of several recent reports.

TABLE III. ASSOCIATION OF DERMATOMYOSITIS WITH MALIGNANT DISEASE (COMPILED FROM THE LITERATURE)

| NUMBER OF CASES | ORGAN OR SYSTEM |
|---|---|
| 25 | Breast |
| 13 | Stomach |
| 12 | Lung |
| 11 | Ovary |
| 10 | Reticuloendothelial |
| 8 | Uterus and vagina |
| 6 | Unknown primary |
| 6 | Gall bladder |
| 5 | Rectum |
| 3 (each) | Colon, kidney, prostate, sarcoma |
| 2 (each) | Esophagus, pancreas |
| 1 (each) | Myeloma, parotid, thyroid, pyriform sinus, larynx |
| Total 117 | |

Schuerrmann[37] estimates that the incidence of malignant disease is five times greater than might be expected on the basis of chance. Christianson and his colleagues[9] deny this and state that both conditions occur in similar age groups. This objection does not take into account the unlikelihood of a person having simultaneously two diseases of relatively brief duration and high mortality. With but few exceptions symptoms related to dermatomyositis have preceded or dominated those of malignancy, and in many cases the tumor was not discovered until after death. Available figures may actually underestimate the frequency of this association, because published series are not restricted to autopsied cases, and instances of malignancy may be missed. Furthermore, none of these series is restricted to adults, and there have been no reports of malignancy among recent reports of 112 cases of dermatomyositis in children, so that the incidence of tumors among adults with dermatomyositis is probably higher than 10 per cent.

Amelioration of musculocutaneous symptoms has followed treatment of the tumor in some cases, but in a few of these there was no relapse of the dermatomyositis as the tumor ultimately progressed. Furthermore, spontaneous remission of dermatomyositis has occurred, and in some cases dermatomyositis followed treatment of the tumor. Therefore, if the relationship between malignant disease and dermatomyositis is not fortuitous, the basis for it is obscure.

*Polymyositis and Nonspecific Myopathies.*—The position of polymyositis in the nosology of muscular diseases is still unsettled. Its differentiation from dermatomyositis on the one hand and muscular dystrophy on the other depends largely upon imprecise criteria.

There is one group of patients whose clinical features are similar to those of dermatomyositis except that dermatitis and calcinosis are absent. The course may be acute or subacute, the distribution of weakness is similar (including oropharyngeal involvement), fever, and other evidence of systemic disease may be present, electromyographic changes are the same, and the histologic lesions in skeletal muscle are identical. In Eaton's important series,[15] it is impressive that 6 of 13 patients who had fever also had skin lesions (stated not to be diagnostic of dermatomyositis) or edema of the eyelids. It might be considered that some of these patients actually had dermatomyositis, but it is equally impressive that an equal number of patients with fever had no skin lesions at all. Because patients with clear-cut dermatomyositis may have a normal muscle biopsy (since the biopsy provides a limited sample of a patchy process), it is not necessary to have a positive muscle biopsy to make the diagnosis of polymyositis if the other features enumerated are present. Some patients presenting this syndrome of polymyositis will ultimately develop the skin lesions of dermatomyositis.

In another group of patients, the course is chronic, systemic signs are absent, oropharyngeal involvement is unusual, and pseudohypertrophy may occur. The clinical picture may resemble any of the forms of muscular dystrophy,[17,48] but electromyographic abnormalities and histologic changes are those of polymyositis. In some cases, spontaneous improvement or apparent response to steroid therapy may occur, and Nattrass[31] has indicated that previous reports of spontaneous improvement of muscular dystrophy may actually have been instances of polymyositis. Most recent authors include the syndrome of "menopausal muscular dystrophy" in this category of polymyositis.

Problems arise when slowly progressive myopathies, which are not familial and have none of the other stigmata of polymyositis, fail to show the histologic changes of polymyositis. Eaton[15] and Walton and Adams[48] include such cases in their series of polymyositis, but in these cases, it seems reasonable to insist upon the presence of characteristic histologic changes. If this is not done, there is no reliable way to distinguish these cases from sporadic or late cases of "limb-girdle" muscular dystrophy. Furthermore, the clinical picture of the endocrine myopathies may be identical with that described for polymyositis.

The difficulty with these cases is that "polymyositis," "myopathy," and "dystrophy" are all probably manifestations of more than one etiologic process. Histologic techniques and clinical features are inadequate to differentiate them,

and until we have more specific diagnostic techniques, there will be differences of opinion. Greenfield, Shy, Alvord, and Berg[19] avoid this problem of nomenclature by classifying such cases as "early adult proximal myopathy," or "late onset proximal myopathy." It may be even simpler to designate this syndrome as "nonspecific myopathy."

*Myopathy or Polymyositis Associated With Systemic Disease.—*

*Collagen diseases:* Similar myopathies, with or without interstitial myositis, may occur in scleroderma and in some cases, a distinction between scleroderma and dermatomyositis may be virtually impossible.[11] The skin lesions of dermatomyositis may also resemble those of systemic lupus erythematosus, and the latter may be associated with myopathy; intermediate forms have been described. Walton and Adams describe one case in which manifestations of all three syndromes appeared at different times. Although widespread involvement of blood vessels and connective tissue is not ordinarily seen in dermatomyositis, there have been reports of pathologic similarities. Furthermore, myopathy may be a major complication of rheumatoid arthritis and, rarely, periarteritis nodosa.

*Carcinomatous myopathy:* The relative rarity of myopathy without skin lesions in malignant disease is in striking contrast to the frequency of dermatomyositis in such patients. The existence of "carcinomatous myopathy" was emphasized by Henson, Russell, and Wilkinson[22] who described 8 cases, all associated with carcinoma of the lung. All had selective involvement of proximal muscles, and a tendency to remit was characteristic. Five of the 8 also had an associated disorder of the central or peripheral nervous system. Postmortem examination was performed in 3 cases, and muscle biopsy in a fourth. Histologic changes suggested myopathy, but were not marked or specific and there was no inflammatory reaction of note. Two patients were said to have responded to neostigmine; one of these had an essentially normal muscle biopsy and might be considered to have had myasthenia gravis, and the other also had signs of polyneuritis.

There have been reports of four other cases of myopathy associated with sensory neuropathy and carcinoma of the lung. Myopathy without neuropathy has been reported in one patient with carcinoma of the pancreas and another with carcinoma of the gall bladder. These are the only cases reported, with the possible exception of 2 cases described as "proximal motor neuropathy" which are incompletely described and may have been myopathies. Two of these additional cases did have an inflammatory response in muscle similar to that of polymyositis.

*Metabolic Myopathies.*—In 1951, McArdle[27] described the single case of a man who complained of painful muscle cramps which were associated with a defect in glycogen breakdown in the muscle. No further instance of this syndrome has been reported since that time. Glycogen storage disease may affect skeletal muscle to such a degree that weakness is very prominent[1]; in such cases, the differential diagnosis is that of "amyotonia congenita." Amyloid deposition in skeletal muscle may be prominent in primary amyloidosis, but the clinical picture is usually that of peripheral neuropathy rather than myopathy.

*Myasthenic Myopathy and Myasthenic Polymyositis.*—There have been isolated reports of patients with clinical features resembling muscular dystrophy in whom neostigmine-responsive and curare-sensitivity could be demonstrated, thus establishing the presence of myasthenia gravis. In addition, a number of patients with the clinical picture of myasthenia gravis prove at autopsy or on muscle biopsy to have lesions indistinguishable from those of polymyositis, and some patients with clinical features of dermatomyositis polymyositis, or carcinomatous myopathy have responded to neostigmine. A syndrome has also been described which is characterized by muscular weakness, loss of tendon reflexes, and sensitivity to curare without response to neostigmine in patients with mediastinal malignancies. Polymyositis refractory to neostigmine occurred in one patient with a thymoma. These complex interrelationships are discussed in detail elsewhere.[36]

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*Endocrine Myopathies.*—

*Thyroid:* Muscular weakness is a common symptom of thyrotoxicosis, and it is sometimes difficult to decide whether this is merely "asthenia" or may justifiably be called "myopathy." Criteria for the latter diagnosis, although not precise, might include: (1) thyrotoxic patients in whom weakness is more prominent than the usual symptoms of hyperthyroidism, and (2) thyrotoxic patients with weakness of selective proximal distribution (in contrast to generalized asthenia), with or without prominent wasting. There seems to be a predilection for men over the age of 40. In the series of Millikan and Haines,[29] weakness of the pelvic girdle was universal, while proximal weakness of the arms was less severe and less frequent. Exophthalmic ophthalmoplegia is present in a minority of cases, and it is unusual for other cranial muscles to be involved. Some cases are said to respond to neostigmine, but Millikan and Haines indicate that these cases might be more appropriately classified as myasthenia gravis.

The pathogenesis is not known. Low serum tocopherol levels may be present in thyrotoxicosis but does not correlate with the degree of weakness. Pathologic changes in the muscle are minimal or absent, although polymyositis occurred in one case.

Although symptoms due to proximal muscle weakness are similar, thyrotoxic myopathy differs from nonendocrine myopathies in two important respects. First, in most of the cases, deep reflexes are either normal or hyperactive. Second, muscular twitching is frequently seen. Both of these signs are usually attributed to disease of the central nervous system; furthermore, creatinuria is often lacking in thyrotoxic myopathy. There are other indications that the central nervous system is involved in the thyrotoxic process; tremor and psychosis are well-recognized complications, and Canary and his colleagues[8] have demonstrated improvement of many of the clinical manifestations of thyrotoxicosis, including strength, after the administration of reserpine, a drug whose primary action is on the central nervous system. The following patient presented a characteristic syndrome of thyrotoxic myopathy but also had marked clonus at knee and ankle.

It is possible that what has been called myopathy is, in part or in some cases, actually a central disorder.

I. H. (P.H. No. 13-60-09). For one year, this 41-year-old waitress began to drop dishes, fell unpredictably, and was able to carry fewer and fewer dinners on her tray. For 6 months, she had trouble climbing stairs and rising from chairs and for a few weeks, she had marked difficulty rising from a kneeling position in church. She had also noted a swelling in her neck which gradually enlarged for 2 years, but she had no other symptoms until 3 weeks before admission, when she began to be upset easily and was conscious of her heartbeat. She lost 6 pounds within a few weeks but had no sweating or heat intolerance.

Her skin was smooth and warm, and her palms were slightly moist. There was diffuse enlargement of the thyroid. She had no tremor or exophthalmos. Cranial muscles were normal. There was weakness of arms and legs, more marked proximally, and relatively more in the legs. She could not rise from a squatting position nor climb onto a chair. There was no wasting or twitching. Deep reflexes were active, and there was clonus at knee and ankle bilaterally, but there were no Hoffman or Babinski signs, and there was no spasticity.

The basal metabolic rate was +35 per cent; radioiodine uptake, 62 per cent in 24 hours; serum protein-bound iodine, 16.0 gamma per cent. Cerebrospinal fluid, roentgenograms of skull and cervical spine, and examination of blood for L.E. cells and sickling tendency were normal.

Following thyroidectomy, she improved steadily, and 3 months later, neurologic examination was entirely normal.

Myopathy may accompany myxedema as well as thyrotoxicosis. One form is associated with enlargement of muscles and slow relaxation ("Hoffman's syndrome"). Thomasen[42] suggests that this is not truly myotonia, because contraction as well as relaxation may be delayed, and other electromyographic differences have been reported, although hyperirritability is common to both conditions. Goldstone and Ford[18] have indicated that, on clinical grounds, the phenomenon may be indistinguishable from myotonia. Enlargement of muscles in infants ("wrestler's syndrome"), with or without delayed relaxation, has been reported under the eponym of Debre-Semelaigne syndrome, but the evidence for hypothyroidism is not conclusive in many of the early cases, and no instance of this syndrome in cretinism has been recorded since the advent of radioiodine and serum protein-bound iodine measurements.

*Adrenal.*—Muscular weakness is prominent in Addison's disease, but this is not usually the picture of myopathy. Hyperadrenalism, however, may be more difficult to differentiate. Among the patients reported by Cushing in the original description of the syndrome which bears his name, there were several who had marked weakness. In most cases, other manifestations of the syndrome usually provide the clue, but in some cases weakness and wasting rather than obesity may dominate.[30] The following patient, reported through the courtesy of Dr. Daniel Sciarra and Dr. Joseph Jailer, was admitted to the Neurological Institute because of weakness. When presented to a Staff Conference of experienced neurologists, the consensus was that he suffered from either a late dystrophy or polymyositis. There were, however, other signs of hyperadrenalism, and as the picture unfolded it became clear that the "myopathy" was only one manifestation of the endocrine disorder.

C. P. (P. H. No. 17-56-48). A 25-year-old man had been a tennis player of tournament caliber, but in the summer of 1953, his legs felt weak and "glued to the court." There was some improvement in the fall, but in December, he began to have marked weakness of the legs and

subsequently of the arms. He also had difficulty holding his head erect. Increasing fullness of the face had been noted despite a loss of 10 pounds during the last few months, and there had been decreased libido which improved somewhat on thyroid medication. Easy bruisability, increased hair on chest, and mild intermittent back pain were symptoms noted only in retrospect.

Examination was normal except for a full round face; there was mild acne on the buttocks, and his blood pressure was 160/100. There was weakness against resistance of all muscles, much more marked proximally, and wasting was noted in similar distribution. Reflexes were normal, and cranial muscles were unaffected.

Laboratory Data: Red blood cells, 5.31 million/cubic millimeter; hemoglobin 16.0 Gm. per cent; diabetic glucose tolerance test. Urinary creatine, 353 mg./24 hours; creatinine, 950 mg./24 hours. Muscle biopsy and cerebrospinal fluid, normal. Urinary 17-ketosteroids, 20-25 mg./24 hours; corticoids, 12.1-15.5 mg./24 hours. Presacral aerogram was inconclusive.

Following subtotal removal of an hyperplastic left adrenal gland, there was clinical and biochemical improvement, but 5 months later he began to complain of weakness of the legs once again. Examination was similar to the original description, and there was metabolic evidence of relapse. A right adrenalectomy was performed, and hyperplastic tissue removed from that side. Since then, during a period of observation of 3 years, his strength has been essentially normal, and no biochemical abnormality has recurred.

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This case has significance not only for the differential diagnosis of myopathy. It underscores the statement of Cope and Raker[10] that "muscular wasting has been the most constant sign in our patients. It leads to fatigue, the most consistent symptom. We would hesitate to make a diagnosis of Cushing's disease if it were absent."

*Parathyroid.*—Muscular weakness has also been recognized as a major symptom of hyperparathyroidism. In a review of 115 cases, Gutman, Swenson, and Parsons[20] noted that pain in the back or extremities was the initial symptom in 72 per cent, but almost a quarter of the patients had muscle weakness or gait disturbance as a major initial symptom. Ordinarily, hyperparathyroidism does not present a problem in neurologic diagnosis, but Vicale[44] presented cases in which differentiation was difficult. In the following case, muscle weakness was the initial and dominant symptom. It was only when falls due to weakness resulted in fractures that bone disease was discovered.

A. B. (P. H. No. 06-51-14). A 48-year-old woman was seen in the clinic in March, 1958, because of increasing stiffness and weakness of the legs which began 2 years previously. In September, 1956, her legs suddenly buckled, and in falling, she incurred a fracture of the left ulna and radius. Weakness of the legs progressed, and she had difficulty raising her feet in walking. She had difficulty rising from chairs and, in the fall of 1957, she had to abandon climbing stairs. She had no pain, and there was no weakness of the arms or cranial muscles. In September, 1957, she had a spontaneous fracture of one rib. Roentgenograms at that time showed diffuse bony demineralization.

Physical examination was normal, save for obesity and diffuse enlargement of the thyroid, in which there was a firm nodule 2 cm. in diameter at the left upper pole. The cranial nerves were normal, and there was no weakness of the neck. There was moderate weakness of shoulder girdle muscles with good strength distally. She waddled in walking and was unable to climb onto a low stool without using her hands. There was marked weakness of the iliopsoas with only slight weakness of distal muscles. Muscular wasting was not detectable; there was no tenderness, and deep reflexes were normal.

Two days later, she was to be admitted to the Neurological Institute, but she fell and fractured the neck of the right femur. An open reduction was performed. Subsequent roentgenographic and metabolic studies indicated the probable existence of hyperparathyroidism. On exploration of the neck, the mass in the thyroid proved to be a parathyroid adenoma, and this was removed.

Her postoperative period was uneventful, but she still had weakness of the legs at the time of discharge 2 months later.

During the preoperative period the following studies were normal: urinary creatine and creatinine excretion, serum enzymes, electromyography, chronaxie and biopsy of deltoid, and vastus lateralus muscles. The lack of abnormality in these tests suggests that the picture of myopathy was due solely to the more generalized metabolic disorder.

## DIFFERENTIAL DIAGNOSIS

The differentiation of syndromes of weakness encompasses a major portion of clinical neurology, but the characterization of a myopathy involves first its differentiation from neural atrophies and from myasthenia gravis, and then its identification among the various myopathies. The clinical features outlined are most important, but muscle biopsy, electromyography and electrical reactions of muscle have come to play an increasingly important role.

In the category of neural atrophies are diseases of the spinal cord and peripheral nerves which, like mycpathies, cause weakness, wasting, and arreflexia. In infancy, the major problem involves resolution of the syndrome of "amyotonia congenita."[6,46] In childhood and adolescence, the major problem is peroneal muscular atrophy (Charcot-Marie-Tooth) which, in characteristic cases, is distinguished by distal weakness, sensory loss, and skeletal abnormalities which do not occur in the usual myopathies. In adults, the major syndrome is amyotrophic lateral sclerosis, which in its full picture, includes pyramidal tract signs that do not occur in uncomplicated myopathy. In the absence of pyramidal tract signs (progressive spinal muscular atrophy), the presence of fasciculation is usually evidence against the diagnosis of myopathy, but this is not absolute. Polyneuritis has to be considered at any age and is usually accompanied by sensory loss.

Problems arise when myopathic conditions start distally[50] or when neuropathic conditions start proximally and are not accompanied by fasciculation or sensory loss. In such cases, electromyography, electric reactions, and muscle biopsy are usually helpful. However, each or all of these aids may fail to resolve the question, or may even be misleading. In some cases, prolonged observation is necessary.

Myasthenia gravis is differentiated on the basis of clinical features and pharmacologic tests. Involvement of extraocular muscles occurs in about 80 per cent of patients with myasthenia and is rare in myopathy. Oropharyngeal weakness is common in myasthenia and rare in all myopathies except the various forms of polymyositis. Abolition of deep reflexes is common in myopathy and does not occur in uncomplicated myasthenia. Fluctuations are common in myasthenia but uncommon in myopathies. Finally, neostigmine-responsiveness and curare-sensitivity are characteristic of myasthenia but not of myopathies. In rare cases, features of both myopathy and myasthenia may be present, both clinically and in terms of electromyographic and muscle biopsy abnormalities.

Polymyositis is distinguished from other myopathies by its clinical features, characteristic changes in biopsy, and may also be differentiated electromyographically. It is to be emphasized that neither the muscle biopsy[1,19] nor the electromyogram[7,35] is pathognomonic, nor do the lack of characteristic changes exclude

the diagnosis if other features are present. Polymyositis may be suspected in rapidly advancing sporadic cases, especially if there is oropharyngeal weakness, if there has been evidence of systemic disease (arthralgia, Raynaud's phenomenon, fever), or if improvement occurs. If there has been edema of the eyelids or a more typical rash, the diagnosis of dermatomyositis is less difficult. The endocrine myopathies are revealed by their distinctive clinical and metabolic features.

None of the biochemical examinations has proved pathognomonic, but when considered with the clinical picture, may be of some value. Creatinuria occurs in both neural wasting and myopathies, and although it is apt to be greater in the latter, this does not serve as a critical distinction. Elevation of serum enzyme activity is more common in myopathy than neural wasting and among myopathies is found most consistently in Duchenne dystrophy and dermatomyositis, but values may be normal in apparently active cases. Ribosuria has not proved a reliable adjunct.

The following tests have been found useful in differential diagnosis of myopathies, especially of sporadic adult cases, but they are obviously subsidiary to evaluation of the history and physical examination: muscle biopsy, electromyography, electric stimulation, urinary creatine and creatinine, serum enzymes, serum calcium and phosphorus, lupus erythematosus cell preparation, electrophoresis of serum proteins, basal metabolic rate, radioiodine uptake, protein-bound iodine. If reflexes are preserved, pharmacologic tests for myasthenia gravis may be indicated, and studies of adrenal function are performed upon specific indication.

## CONCLUSION

Despite many advances, knowledge of muscular diseases is grossly imperfect. Classification is unsatisfactory and debated by different authors. Pathogenetic mechanisms are not known for any of these conditions. Treatment is essentially supportive and symptomatic, except in endocrine myopathies. It is to be hoped that developments in biochemistry, experimental pathology, and pharmacology will ultimately provide answers to perplexing questions relating to diseases with frequently tragic implications.

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## Erratum

In the article by Neil I. Gallagher, M.D., and William A. Knight, Jr., M.D., entitled "Evaluation of Amphetamine as an Appetite Depressant," which appeared in the August issue of the JOURNAL, pages 244-252, the following corrections should be noted:

On Fig. 3 and 4, mg./ml. should be changed to mg./100 ml. This same correction should be made three times on Tables III and IV at the bottom of column 1.

The last complete sentence on page 249 should read as follows:

"Fasting specimens showed less than 0.005 mg. amphetamine per 100 ml. serum, which is insignificant and within the limits of experimental error of the method."

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# MYASTHENIA GRAVIS

## Current Status of Pathogenesis, Clinical Manifestations, and Management

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MYASTHENIA gravis is a chronic disease characterized by weakness and abnormal fatigability of skeletal muscle. The muscles innervated by the cranial nerves are particularly affected, and usually those of the neck, trunk, and extremities. In severe cases, weakness of the muscles of respiration occurs. Smooth and cardiac muscles are not involved. The disease usually becomes generalized, but in a minority of cases it remains localized to the extraocular muscles. The symptoms are commonly ameliorated, although to a variable degree, by anticholinesterase compounds. This response serves as the basis for diagnosis and management of the disease.

### HISTORY

The symptoms of myasthenia gravis were first described by Thomas Willis in 1672.[1,2] Two hundred years later Erb[3] recognized its tendency to spontaneous remission, and Goldflam[4] the fluctuating nature of the symptoms. Jolly[5] and Oppenheim[6] described the progressive failure of affected muscles to respond to repeated faradic stimulation, to which the term "myasthenic reaction" was applied, and Hoffmann[7] showed that this reaction was more marked at higher frequencies of nerve stimulation. It was Jolly[5] who named the disease "myasthenia gravis pseudoparalytica." Oppenheim's monograph, published in 1901,[8] still remains the classical description of the disease, although later reviews further delineated its natural course.[9-13] In 1901, Lacquer and Weigert[14] first described the association of thymic tumor with myasthenia gravis, and in 1917, Bell emphasized the high incidence of hyperplasia of the thymus.[15] Mary Walker, in 1934, introduced the use of anticholinesterase compounds in the diagnosis and management of the disease.[16] In 1941, Harvey and Masland,[17] employing quantitative electromyographic techniques, demonstrated the similarity between the defect in neuromuscular transmission in myasthenia gravis and that produced by curare,[18] and Blalock and Harvey[19] published the first reports of the effect of thymectomy on the course of the disease.

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PATHOLOGY

Pathologic changes in this disease are virtually limited to hyperplasia or tumor of the thymus gland, and scattered collections of lymphocytes (lymphorrhages) in the muscles.

*Thymus.*—Of 300 patients with generalized myasthenia gravis who have been followed in the Johns Hopkins Hospital, the thymus has been examined following thymectomy in 53 and post-mortem examination in 20 (Table I). It was found to be abnormal in 83 per cent, being hyperplastic with lymphoid follicle ("germinal center") formation in 48 per cent, enlarged but normal microscopically in 7 per cent, and either containing or replaced by a thymoma in 29 per cent. In 17 per cent the thymus was either normal in gross and microscopic appearance or not identifiable in the mediastinal fat, a normal finding in adults. In approximately three-fourths the thymus contained numerous germinal centers, which are absent[20] or rare[21] in individuals who do not have myasthenia gravis. Thymic hyperplasia was more common in female patients and thymoma in males.

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The thymomas varied greatly in size, from 2 cm. in diameter to massive tumors occupying nearly half the thoracic cavity. They were usually surrounded by a dense fibrous capsule and separated into lobules by fibrous trabeculae. The tumor was usually discreet, but in 6 patients it invaded adjacent structures. In 2 of these it gave rise to implants in the pleura and, in 1, in the bronchi, apparently as a result of direct extension. In no instance was there any evidence of distant metastasis. In several patients there were areas of necrosis in the tumor, and in a few calcification which could be seen roentgenographically. The tumors were composed of varying numbers of epithelial cells, lymphocytes (or "thymocytes"), and connective tissue cells. Cells with large pale nuclei were common, and mitotic figures were occasionally seen, leading to the histologic diagnosis of "malignant" tumor, although there was no correlation between the histologic appearance and local invasiveness, and distant metastases were never seen.

TABLE I. STATUS OF THYMUS IN 73 ADULT PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

| | THYMUS EXAMINED FOLLOWING: | THYMECTOMY | | POST-MORTEM | TOTAL |
|---|---|---|---|---|---|
| | PRESENT STATUS OF PATIENT: | LIVING | DIED OF M.G. | DIED OF M.G. | |
| Status of Thymus | Hyperplasia | 24 | 7 | 4 | 35 |
| | Persistent | 1 | 1 | 3 | 5 |
| | Normal | 3 | | 4 | 7 |
| | None | 2 | | 3 | 5 |
| | Thymoma | 6 | 9 | 6 | 21 |

The presence of large numbers of germinal centers was the only thymic abnormality pathognomonic of myasthenia gravis.[20,21] A few germinal centers have been found at post-mortem examination in the thymus of 10 per cent of nonmyasthenic subjects, and in about one-third of patients with hyperthyroidism,

Addison's disease, and acromegaly.[21] Hyperplasia of the thymus occurs in approximately the same porportion of patients with these diseases and may also occur following castration.[21] Thymomas resembling those found in myasthenic patients occur, although rarely, in nonmyasthenic subjects. Six such tumors have been observed in 800,000 hospital admissions and 24,000 autopsies performed in the Johns Hopkins Hospital. One of these patients had Addison's disease. Another developed myasthenia gravis 5 years after a large well-encapsulated thymoma was removed, presumably completely.[23] A similar occurrence has been reported after complete[24] and incomplete[25] removal of a thymoma. In a series of 45 patients with thymoma reported by Seybold[22] three-fourths had myasthenia gravis. The great majority were located in the anterior mediastinum, anterior to the arch of the aorta, but a few were discovered posteriorly in the thorax, at any level down to the diaphragm, and even in the lung.[26] One-fourth contained sufficient calcium to be apparent radiologically.

In contrast to nonmetastasizing thymomas, which are found mainly in myasthenic patients, malignant thymic tumors with distant metastases occur in nonmyasthenic subjects.[27] Ten such tumors, all described as carcinoma of the thymus, occurred in 24,000 autopsies. None was associated with myasthenia gravis.

*Skeletal Muscle.*—In approximately two-thirds of the 37 patients who died of myasthenia gravis and came to post-mortem examination (Table I) there were scattered lymphorrhages in the skeletal muscle. These consisted of compact groups of mononuclear leukocytes, predominantly lymphocytes, but sometimes including plasma cells and histiocytes, usually surrounding a capillary or venule. The muscle fibers usually appeared normal; occasionally there were focal areas of atrophy and rarely of necrosis, with surrounding inflammatory reaction. In one-third of the patients, muscle which had been severely affected by the disease appeared entirely normal on histologic examination.

The histologic changes in skeletal muscle of myasthenic patients (lymphorrhages and less prominent necrosis and atrophy) have been carefully studied by Russell,[28] who felt that there was a correlation with the clinical evidence of functional change. There is general agreement that the histologic changes are not pathognomomic of myasthenia gravis, since similar changes, including lymphorrhages, may be found in many other disorders affecting the neuromuscular system, including polymyositis, dermatomyositis, scleroderma, muscular dystrophy, myotonic dystrophy, progressive muscular atrophy, peripheral neuropathy, hyperthyroidism, and Addison's disease.[29-32] No consistent abnormality has been found in special staining of nerve endings[33] or muscle cholinesterase.[34]

*Cardiac Muscle.*—This is usually normal histologically, but some instances of round cell infiltration and even necrosis, resembling the changes in skeletal muscle, have been reported.[28,35,36]

*Other Organs.*—These are characteristically normal, although lymphocytic infiltrates in the liver, thyroid, adrenals, and other organs have been reported to occur.[30] Of the patients who died and were examined post-mortem (Table I), 8 had some abnormality of the adrenal cortices (5 enlargement, 2 atrophy, and

1 focal necrosis), possibly attributable to intercurrent infection or terminal cachexia. Six had some abnormality of the anterior lobe of the pituitary (1 enlargement, 3 chromophobe adenoma, 1 hyperplasia of chromophobe cells, and 1 cyst), but similar changes are found in patients succombing to a variety of diseases. An excess of acidophilic substance has been reported to occur in the anterior lobe,[37] but this has not been confirmed.

PATHOPHYSIOLOGY

*Normal Neuromuscular Transmission.*—Resting muscle fibers normally have a potential difference of approximately 90 mv. between the two sides of the surface membrane, the inner surface being negative with respect to the outer. They are, therefore, said to be in a state of "polarization." When a nerve impulse reaches the motor-nerve endings, acetylcholine (ACh), the normal mediator of neuromuscular transmission is released. This compound causes a disappearance (actually a slight reversal) of the potential difference across the muscle membrane in the end-plate region adjacent to the motor nerve ending[38] (Fig. 1). The cell

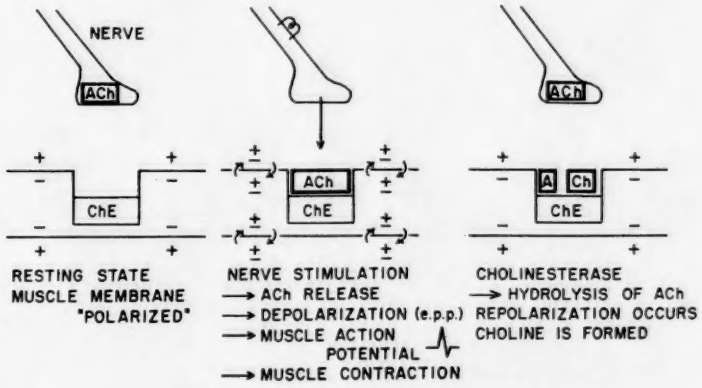


Fig. 1.—Normal neuromuscular transmission.

membrane is said to have become "depolarized." This depolarization is propagated along the muscle membrane as a wave of increased negativity, termed the muscle action potential. This in turn initiates contraction of the muscle fiber. Shortly after ACh has initiated depolarization of the end-plate, it is hydrolyzed into acetate and choline by cholinesterase enzyme concentrated in the muscle at the end-plate region. The potential difference across the entire muscle membrane is then restored; i.e., repolarization occurs, and the muscle is thereby made ready to be depolarized again.

*Causes of Neuromuscular Block.*—Disturbance of neuromuscular transmission may result from interruption of the normal sequence of events at any step. In most instances, neuromuscular block occurs as a result of either deficient or excessive action of ACh on the motor end-plate, or as a result of drugs or disease which simulate these effects.[39]

*Deficient action of acetylcholine:*

1. Deficient release of ACh from the motor nerve endings is believed to be responsible for the weakness of botulinus poisoning.[40]

2. Inhibition of the depolarizing action of ACh on the motor end-plate ("acetylcholine-inhibitory block") occurs in at least three situations:

a. Block occurring without change in the resting potential of the muscle membrane, and reversible by ACh or anticholinesterase compounds. The block produced by d-tubocurarine is of this type.[41] This drug is believed to exert its effect by competing with ACh for receptor sites at the end-plate, so that the resulting block has been termed "*competitive.*" This type of block is characterized by inhibition of the depolarizing action of injected ACh, and by reversal of the block following the injection of sufficient ACh or anticholinesterase compound (Fig. 2).

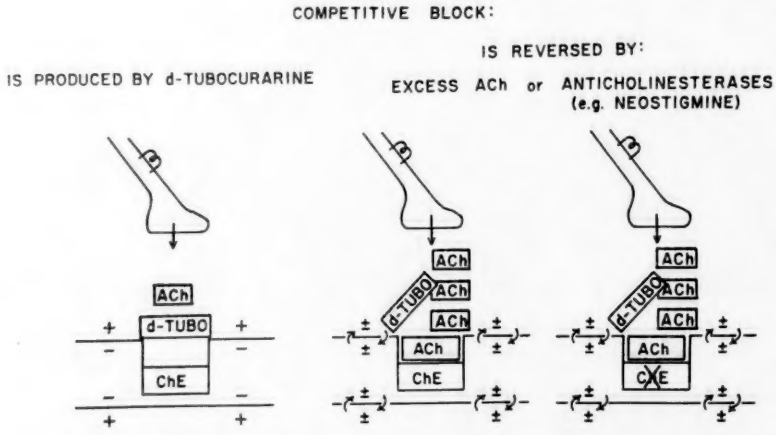


Fig. 2.

b. Block not associated with any change in membrane potential, but not reversible by ACh: This type of block occurs several minutes after the exposure of frog muscle to ACh, and persists even after recovery of the muscle membrane from the initial depolarization. It is attributable to the development of refractoriness of the motor end-plate to ACh.[42]

c. Block associated with hyperpolarization of the muscle membrane: The weakness of hypokalemia is probably due in part to this mechanism, resulting from an increase in the ratio of intracellular to extracellular concentration of potassium.[43]

*Abnormally prolonged depolarization in the region of the end-plate:* When this region is in the depolarized state, it becomes inexcitable. This type of block is produced by an excessive concentration of ACh, by anticholinesterase compounds, by choline, and in most animal species by decamethonium and succinylcholine.[44,45] There is characteristically no inhibition of the depolarizing action of injected ACh or anticholinesterase compound; in fact, these intensify the

block by their additive effect (Fig. 3). Neuromuscular block which is non-ACh-inhibitory and non-ACh-reversible (i.e., "noncompetitive") is frequently presumed to be of the depolarizing type, but confirmation of such a mechanism requires measurement of the membrane potential in the region of the end-plate. This measurement has only recently been made in man[46] and has not yet been applied to the study of disease or drug action.

*Mixed types of block:* The effect of some chemical agents, such as decamethonium, on neuromuscular transmission varies in different species, and even in different muscles. In some instances, a neuromuscular block results which has some properties of both the competitive and depolarizing types.[47]

*Mechanism of Neuromuscular Block in Myasthenia Gravis.*—A single supramaximal stimulation of the nerve to affected muscle evokes a muscle action potential and twitch that are below the normal range only in muscles that are severely affected by myasthenia gravis.[48] However, in all muscles affected by the disease, repetitive stimulation at frequencies that normally produce responses of even amplitude results in progressive decline of these responses (Fig. 4). The degree and rate of decline vary with the frequency of nerve stimulation and with the degree of involvement of the muscle by the disease. In an occasional patient,

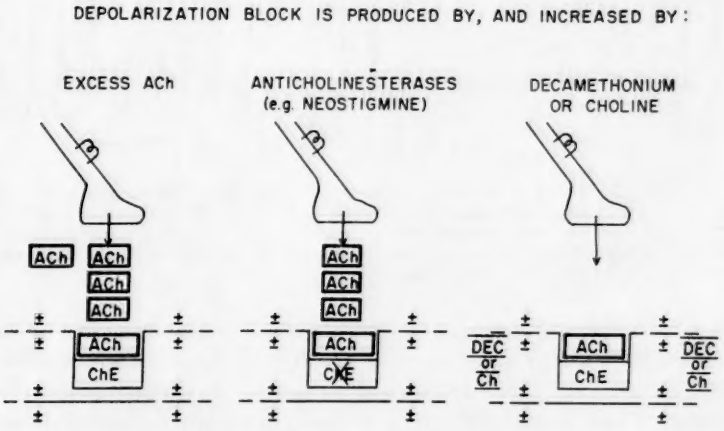


Fig. 3.

the response to the first few stimuli increases progressively, a phenomenon that has been termed neuromuscular facilitation. Both the facilitation and depression are restored toward normal by the administration of neostigmine or one of the other anticholinesterase compounds.[17] Similar alterations in neuromuscular transmission occur in normal subjects following the administration of d-tubocurarine.[41]

Since there is no known abnormality of central neural or peripheral nerve function in myasthenia gravis, and since the evidence for a defect in muscle contractility[49,50] does not appear to be conclusive, the manifestations of this

disease are believed to be due primarily to impairment of neuromuscular transmission. At present the evidence suggests that the defect in neuromuscular transmission is due to some alteration in the ACh mechanism. This could result from (1) an excessive concentration of cholinesterase at the neuromuscular junction, (2) failure of each nerve impulse to release a normal quantum of ACh, or (3) elevation of the excitatory threshold of the motor end-plate to the ACh release by each nerve impulse. There is no evidence for excessive cholinesterase activity in the muscle of myasthenic patients.[51] Recent studies support the

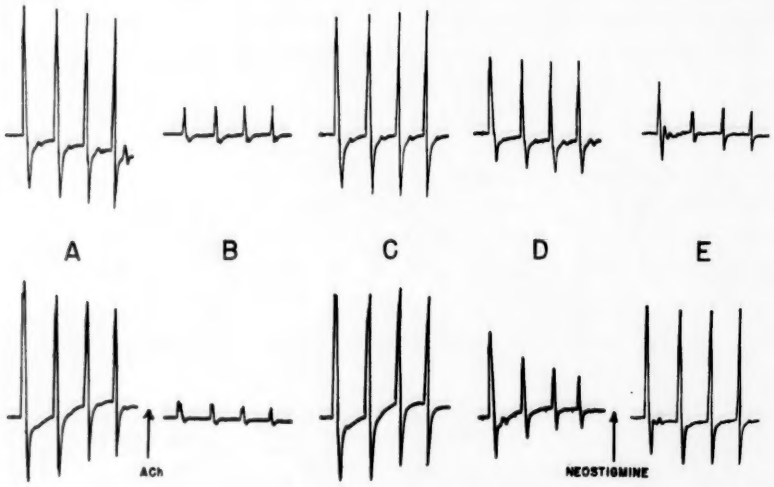


Fig. 4.—Effect of ACh and neostigmine on the muscle action potential response to nerve stimulation in a normal subject (upper row) and a patient with myasthenia gravis (lower row). *A*, control response to four supramaximal nerve stimuli at 40 millisecond intervals; *B*, prompt depression 7 seconds after the intra-arterial injection of 5 mg. ACh; *C*, recovery 15 seconds after injection; *D*, late depression one hour after injection; *E*, effect of 0.5 mg. neostigmine.[52,53]

third possibility and indicate that the defect in neuromuscular transmission in myasthenia is due to a competitive (ACh inhibitory) block, similar to that produced by d-tubocurarine in normal subjects. In myasthenic patients the block appears to be produced by ACh released in a normal manner during neuromuscular transmission, or by choline or a closely related compound formed following the hydrolysis of the naturally released ACh. The intra-arterial administration of either ACh or choline to myasthenic patients results in an impairment of neuromuscular function which is characterized by inhibition of the depolarizing action of ACh and reversal by anticholinesterase compounds (Figs. 4 and 5).[52] This competitive blocking action is in contrast to the predominantly noncompetitive block produced by these compounds in normal subjects, in whom the blocking action is intensified by anticholinesterase compounds.[53] It is not clear whether the myasthenic block is the result of an abnormal response of the end-plate to substances normally released from the motor nerve endings, or to the formation of an abnormal product of acetylcholine or choline having a competitive blocking action.

Reports of demonstration of a substance in the blood[54] or thymus[55-58] of myasthenic patients capable of producing neuromuscular block in experimental animals, and of a substance in serum capable of inhibiting the synthesis of acetylcholine,[59] have not been confirmed.[60-63] In this regard, it is of interest that curare itself is rapidly removed from the blood stream and fixed in the tissues.[64] Exchanged transfusions between myasthenic and nonmyasthenic subjects have no effect on the strength of either.[65]

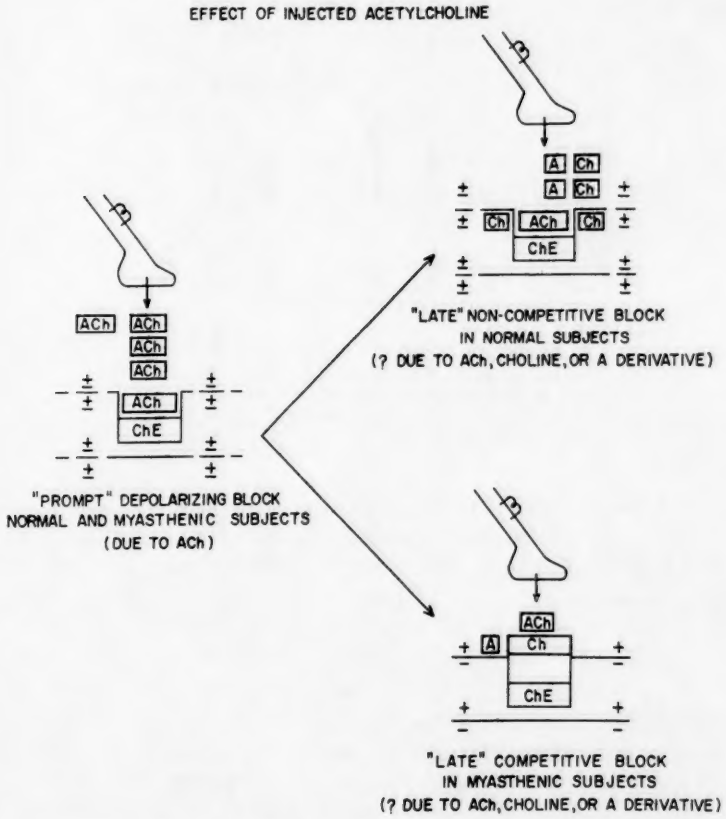


Fig. 5.—Effect of ACh in normal subjects and patients with myasthenia gravis. Prompt depolarizing block occurred in both (left). This was followed by a late noncompetitive block in normal subjects and a competitive block in myasthenic patients (right).

## CLINICAL MANIFESTATIONS

The *incidence* of generalized myasthenia gravis is slightly higher in females, while localized ocular myasthenia gravis is slightly more common in males. The disease has no limitation with regard to geographic distribution or racial incidence, although it tends to begin at an earlier age in colored patients. *Onset*

of the disease may occur at any age, but tends to be at an earlier age in female patients than in male patients, the average age of onset being 28 years in the former and 42 in the latter.[11] In children and adolescents, the disease is much more common in female patients. The incidence of onset of generalized myasthenia reaches a peak in the third decade in women, while in men it is fairly uniform from the third through the seventh decade (Fig. 6). After the age of 60, onset of the disease is much more common in men.

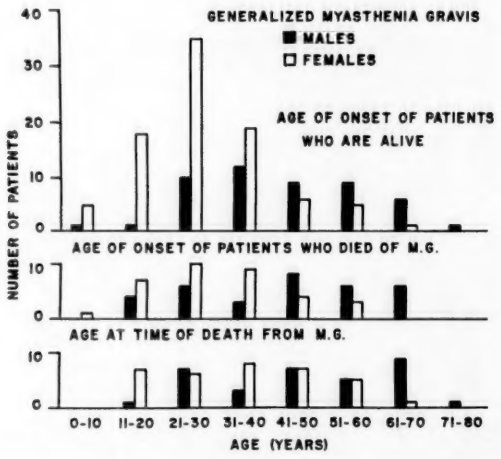


Fig. 6.

*Initial Manifestations.*—These are most commonly referable to the extraocular muscles. In 300 patients with generalized myasthenia gravis the initial symptom was ptosis in 26 per cent, diplopia in 24 per cent, blurring of vision in 3 per cent, weakness of legs in 13 per cent, generalized fatigue in 6 per cent, difficulty in swallowing in 6 per cent, slurred and nasal speech in 5 per cent, difficulty in chewing in 4 per cent, weakness of arms, hands, neck, or face in each of 3 per cent, and weakness of trunk or shortness of breath in 1 per cent. Symptoms were usually gradual in onset, but occasionally there was sudden onset of weakness of one muscle or group of muscles, or rarely of generalized weakness.

*Extraocular Muscles.*—The extraocular muscles were affected at some time in the course of the disease in almost every patient. Muscle weakness occurred unilaterally or bilaterally, and in almost all combinations of functional disturbance. The levators of the lids and upward deviation of the eyes were usually most affected, and downward deviation least affected. Occasionally, there was complete limitation of extraocular movement. When diplopia was not pronounced, it was sometimes described as a blurring of vision. Occasionally, the visual image was suppressed in one eye, so that diplopia was not present, despite a marked divergence of extraocular movement. The ocular symptoms tended to vary from day to day, as did the other manifestations of the disease.

When ptosis was present, the orbicularis oculi were also usually affected, resulting in weakness of closure of the lids. Rarely retraction of the lids occurred,

with or without exophthalmos. Retraction was usually unaffected by anticholinesterase medication, but an instance of improvement by this medication has been reported.[66] Pupils and visual fields and acuity were never affected, and difficulty in accommodation was rare.[67]

*Localized Ocular Myasthenia Gravis.*—Of 380 patients with myasthenia gravis who have been followed for an average period of 10 years, the disease has remained localized to the extraocular muscles in 20 per cent, except for concomitant involvement of the orbicularis oculi. This localized ocular form of myasthenia gravis was slightly more common in male patients, in contrast to the generalized form, and tended to begin at an older age.[11]

*Generalized Myasthenia Gravis.*—In 80 per cent of the patients the disease progressed to involve numerous muscles and usually became generalized. The most frequent sequence of involvement was: extraocular muscles, followed by muscles of the face, swallowing, speech, jaw, tongue, neck, shoulders, arms, hands, hips, upper legs, lower legs, trunk, and respiration. However, this sequence was not invariable, and it was not uncommon for the muscles innervated by the cranial nerves to be severely involved with little or no weakness of the extremities or trunk. Occasionally, the reverse was seen. Progression of the disease usually occurred over a period of weeks or months, less often over a period of years. At the end of the first month after appearance of symptoms, the disease had become generalized in 40 per cent, and was still limited to the extraocular muscles in 34 per cent, to the bulbar musculature in 15 per cent, and to the extremities in 11 per cent. Of the 116 patients whose symptoms were confined to the eyes for a period of one month, 30 per cent developed generalized myasthenia within 6 months, 60 per cent within 5 years, and 75 per cent within 10 years. In one patient, extension of the disease occurred after 24 years of localized ocular myasthenia. Twenty-five per cent have continued to have localized ocular myasthenia gravis for an average period of 10 years.[10]

When a patient who has localized ocular myasthenia gravis is examined, the question arises as to the likelihood of extension of the disease to other muscles. When the duration of symptoms is brief, the course cannot be foreseen, but when ocular symptoms have been present for two years or longer without evidence of extension beyond the orbicularis oculi, it is probable that the disease will remain localized.

The patient with the typical features of generalized myasthenia gravis had ptosis, resulting in a characteristic sleepy appearance, sometimes accompanied by compensatory wrinkling of the forehead (Fig. 7). Facial weakness caused an apathetic, "myasthenic" expression, and orbicularis oris weakness a smirk or "snarl" when smiling or laughing was attempted. When the frontalis was severely affected, it was impossible to wrinkle the forehead, and when the orbicularis oculi were very weak, the eyes could not be shut. Weakness of the masseters caused sagging of the jaw (Fig. 8), which often had to be supported by the hand. There was difficulty swallowing, with nasal regurgitation and choking spells, and difficulty speaking, with nasal slurred speech. Weakness of the neck muscles was frequent, and severely ill patients had to support their head. The upper extremities were usually affected before the lower and the proximal muscles

Fig. 7.—A 64-year-old woman with localized ocular myasthenia gravis of 3 years' duration, illustrating severe ptosis with compensatory wrinkling of forehead, divergent strabismus, and incomplete response to neostigmine (2 mg. intramuscularly) (right).

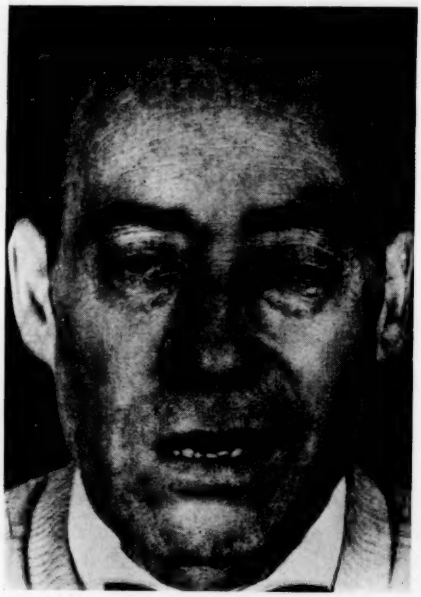

Fig. 8.—A 54-year-old man with severe generalized myasthenia gravis of two years' duration, illustrating ptosis, divergent strabismus, facial weakness, and sagging of jaw.

before the distal ones, so that among the early complaints were difficulty in shaving and combing the hair. In the upper extremities, the extensors were usually involved before the flexors and to a greater extent, while in the lower extremities the reverse usually occurred. Wasting of mild to moderate degree occurred in muscles which had been severely affected for a prolonged period of time, probably as a result of disuse. Inanition and bed rest promoted atrophy. The deep tendon reflexes were not affected. The muscles of the trunk and abdomen and of respiration were among the last involved after the disease had become severe. There then occurred shortness of breath, particularly on exertion, and difficulty in coughing, which might become extremely troublesome during respiratory infections, resulting in pooling of secretions in the respiratory tract, bronchitis, atelectasis, and pneumonitis. Death was usually the result of failure of the muscles of respiration, or, less often, respiratory obstruction following aspiration of food. In some patients who died suddenly the precise cause could not be ascertained.

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Sensory complaints were uncommon, although 10 per cent of the patients noted occasional numbness or tingling in the extremities or face, and 5 per cent complained of pain and soreness in the muscles of the neck, back, or legs, attributable to weakness of postural muscles. Occasional instances in which the presenting complaint was primarily orthopedic, due to faulty posture and gait, have been reported.[68] Mild headache or eye pain dve to ocular imbalance occasionally occurred.

Weakness usually became worse with repeated effort of the involved muscles, so that most patients were at their best strength in the morning and weakest in the evening. Rest was usually followed by partial recovery of function. However, in most cases some of the muscles had a continually reduced function, so that some weakness was present even on awakening. In a few patients, the strength was virtually the same throughout the day.

*Course.*—The course of the disease was variable. In the majority of patients there was gradual extension of the involved areas leading to a relatively steady state of weakness which remained unchanged for many years, with the exception of moderate fluctuations in severity. The basic level of weakness was usually reached within the first 3 years after onset, most often within the first year (Fig. 9). In patients who developed severe myasthenia, the average interval between onset of the disease and the first severe episode was 8 months. This interval was shorter in male patients, in whom the disease was more likely to progress rapidly than in female patients. Of 300 patients with generalized myasthenia gravis who have been followed for an average period of 10 years, 30 per cent died of the disease 3 months to 25 years after onset, with 70 per cent of the deaths occurring within one year after onset and 85 per cent within three years.[11] Most patients who survived beyond 3 years were likely to continue with a chronic form of the disease for many more years. Thirteen per cent of the entire group are in complete or nearly complete remission at the present time, 26 per cent have had some improvement since their first severe episode of weakness, 21 per cent are unchanged, and 10 per cent have become worse.

*Remission.*—Symptoms of the disease tended to fluctuate in severity from day to day or at longer intervals in almost all patients, and approximately one-fourth had a remission lasting at least 6 months, with complete or nearly complete disappearance of signs and symptoms. In some patients mild ocular symptoms persisted during the remission, and in others these recurred from time to time, particularly after emotional stress or upper respiratory infection. Others had mild "fatigability" which did not require medication. Most patients had only one remission, while 10 per cent had two to four.[11] Half of the remissions began during the first year of illness, but others occurred after as many as 17 years, and the average interval between onset of the disease and remission was 4 years. The duration of remission varied up to 18 years, with an average of 4.6 years. Both incidence and duration of remission were greater in women and in younger patients. The duration was approximately the same in patients whose period of amelioration occurred early in the disease as in those in whom it began late. The administration of anticholinesterase medication did not appear to influence the incidence or duration of remission. The episodes of relief that were observed resembled those described in other series.[9,12,13]

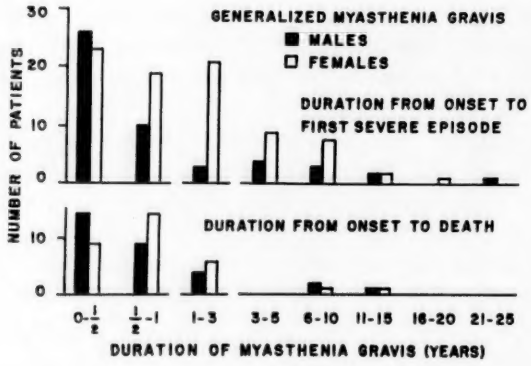


Fig. 9.

*Exacerbation.*—The factors most commonly associated with exacerbation of the disease were upper respiratory infection, other infectious illnesses, emotional tension, and the post-partum period. In addition, most women felt weakest for several days to 2 weeks before each menstrual period. They were usually at their best strength during or shortly after the menstrual period. Sometimes exacerbation of the disease occurred without evident cause. Occasionally it was followed by a remission.

*Thymus.*—A thymoma was present in 29 per cent of the 73 patients in whom the thymus was examined following thymectomy or post-mortem examination (Table I). Most patients who had a thymoma had more severe and rapidly progressive myasthenia, and the mortality rate of these patients from the disease has been 70 per cent, compared to 40 per cent for patients whose anterior mediastinum has been examined without revealing a tumor (Table I) and 30 per

cent for the entire group of patients. Of those patients who are still alive and in whom the status of the thymus is known as a result of operation, 17 per cent had a thymoma, while of those patients who have died of the disease 41 per cent had a tumor. However, there has not been any consistent correlation between the observed changes in the thymus and the clinical course of the disease. Three patients with a thymoma had a mild form of the disease for many years; one died of an unrelated retroperitoneal sarcoma after 20 years of mild myasthenia, and another developed a complete remission of myasthenia prior to thymectomy. It may be of interest that the thymoma in the latter patient was partly necrotic. In 3 patients who died of myasthenia gravis after a severe illness of one-half to 7 years' duration, no thymic tissue could be detected at post-mortem examination.

Thymomas could be seen roentgenographically in almost all instances, best in the lateral view of the anterior mediastinum and occasionally with the help of lateral tomograms. Thymus glands that were enlarged but free of tumor could not be seen. In spite of the large size of many tumors, only 6 patients had local symptoms, due to bronchial compression in 4 (with bronchiectasis in 2), pleural implants in 1, and tumor necrosis resulting in bilateral pleural effusion in 1.

The incidence of thymoma in patients with myasthenia gravis is undoubtedly less than the 29 per cent observed (Table I) and reported,[20] since patients with a tumor are more likely to be operated on, and they are also more likely to die of the disease. Four patients had roentgenologic evidence of a mass in the anterior mediastinum, but have not yet been operated on. Thus at least 8 per cent of the 300 patients with generalized myasthenia, or 7 per cent of the 380 patients with generalized or localized myasthenia, have had a thymoma. The true incidence of thymoma in myasthenia gravis is somewhere between 7 and 29 per cent. A roentgenographically demonstrable mass in the anterior mediastinum has been reported to occur in as many as 15 per cent of myasthenic patients.[22]

*Pregnancy.*—The effect of pregnancy on the course of the disease was variable. In most instances there was no effect. The commonest change was moderate exacerbation at some time during a 6-week period after delivery, which occurred in about one-third of 34 pregnancies in 24 patients.[11] Less often there was moderate improvement during pregnancy, occurring in one-fourth, usually during the latter half. Occasionally (in about one-sixth) there was exacerbation of the disease during pregnancy, usually during the first trimester. The early reports of a high incidence of remission during the latter half of pregnancy[69] have been followed by reports of less frequent remission,[70] and even of exacerbation.[71]

*Neonatal Myasthenia Gravis.*—Children born of myasthenic mothers do not develop the classical progressive form of the disease, although occasionally they are weak for from several hours to 7 weeks after delivery and may require anticholinesterase medication during this period. One instance of neonatal myasthenia was observed in 34 deliveries. This occurred even though the mother was in partial remission of her disease several years after thymectomy had been performed. A total of 27 infants with neonatal myasthenia have been described in the literature.[71-78] Recovery was complete in all but one infant who died despite the administration of anticholinesterase drug. There has been

no correlation between the occurrence or severity of neonatal myasthenia and the duration or severity of the mother's illness, or the status of her thymus.

*Childhood Myasthenia Gravis.*—Ten per cent of patients with generalized or localized ocular myasthenia gravis had onset of the disease during childhood. When the disease began in childhood it tended to be more symmetric in distribution and more widespread, but there was generally slower progression and a higher incidence of remission than in adults. Ophthalmoplegia tended to be more marked and often responded to anticholinesterase medication even less than in the adult. There was one instance of occurrence of the disease in siblings, in four brothers who have had generalized myasthenia since infancy. An even higher frequency of sibling incidence has been reported.[74]

*Thyroid Function.*—Three per cent of the myasthenic patients studied had associated hyperthyroidism, and 2 per cent had exophthalmos in the absence of thyroid disease or a history of thyroid disease.[11] The incidence of these associations was higher than would occur by chance. Treatment of the hyperthyroidism was usually followed by improvement in the myasthenia, and when hyperthyroidism recurred in one patient there was an exacerbation of the myasthenia. In addition, myasthenia gravis developed in 3 euthyroid patients during dessicated thyroid administration for weight reduction, and, in another euthyroid patient who had ocular myasthenia gravis and exophthalmos (postthyroidectomy), administration of this drug in an effort to reduce the exophthalmos was followed by fulminating generalized myasthenia which terminated fatally. On the other hand, 6 euthyroid myasthenic patients received dessicated thyroid without effect on their strength. A diverse relationship occurred in 3 patients in whom myasthenia gravis appeared 1 month and 3 and 7 years after subtotal thyroidectomy.

Numerous authors have described a relationship between the onset or severity of myasthenia gravis and disease of the thyroid gland. Myasthenia may have its onset during elevated thyroid activity or appear after treatment when the patient is euthyroid.[75-77] It has been reported both to have been improved and made worse by treatment of existing hyperthyroidism or the administration of dessicated thyroid to a euthyroid individual.[78-82] Because generalized muscular weakness and impairment of extraocular movement are common in hyperthyroidism, it is probable that some instances of association of the two diseases are overlooked. In the great majority of patients with hyperthyroidism and weakness, the response to neostigmine is normal, excluding the presence of associated myasthenia gravis.

*Cardiovascular Function.*—There was no clear-cut evidence of any alteration in cardiovascular function attributable to myasthenia gravis. In one patient with severe myasthenia who was in a body respirator and had a sudden fall in blood pressure to shock levels, the pressure returned to normal coincident with the intravenous injection of neostigmine and atropine, but the cause of these changes was not clear. The administration of anticholinesterase medication sometimes produce bradycardia and a slight reduction in blood pressure, but these effects were less marked than in nonmyasthenic subjects, in whom a profound reduction in pressure occasionally occurs.[83] Atropine often produced

tachycardia. Electrocardiographic changes unrelated to medication have been reported in a few myasthenic patients,[84,85] but coronary arteriosclerosis and other causes of heart disease were not excluded.

*Laboratory Data.*—No alterations could be detected in the chemical constituents of the blood or urine that were determined, except for mild creatinuria in some bedridden patients. Minor alterations in plasma proteins,[86] and an abnormally low level of serum complement[87] have been reported. In only 1 patient were there alterations in the cellular components of the blood that were not attributable to intercurrent infection or blood loss. This patient was a 48-year-old woman with mild myasthenia gravis, a thymoma of at least 7 years' duration, and severe bone marrow aplasia with anemia, leukopenia, and thrombocytopenia of 2 months' duration. Death occurred 2 days after thymectomy without any change in the blood picture. Fourteen other instances have been reported of the simultaneous occurrence of benign thymoma and refractory anemia, accompanied in some by thrombocytopenia or leukopenia.[88,89] Only 3 of the patients had myasthenia gravis. The blood picture improved following thymectomy in 4 of 10 patients, and in two, in whom there appears to have been hemolytic anemia in addition to bone marrow agenesis, there was some improvement following splenectomy or the administration of adrenal cortical or adrenocorticotropic hormone.

*Diagnosis.*—A presumptive diagnosis could generally be made on the basis of the history, distribution, and usual fluctuating nature of the weakness, and by the usual increase in weakness that occurred on repeated effort of involved muscles. The diagnosis was confirmed by the improvement in strength which characteristically occurred following the administration of an anticholinesterase compound such as neostigmine (Prostigmin)[90,91] or edrophonium (Tensilon)[92,93] when the patient was in a "basal" state at least 6 hours after the last medication. The improvement was often incomplete even after maximum doses (Fig. 7), but careful measurement and recording of the level of strength revealed a significant change in all except a few patients with localized ocular myasthenia and a rare patient with generalized myasthenia. In these a response could sometimes be elicited later in the course of the disease. Unequivocal increase in strength following neostigmine did not occur in patients who were not considered to have myasthenia gravis, with the exception of 4 patients with ptosis and limitation of extraocular movement due to multiple sclerosis or arteriosclerotic cerebral vascular disease,[11] and 1 with generalized weakness due to disseminated lupus erythematosus. An increase in strength has also been reported in a few patients with polymyositis or carcinomatous neuropathy or myopathy.[94] These responses have been slight and sufficiently unusual to detract little from the diagnostic value of the test.

The width of the palpebral fissures was noted with the eyes at rest and after one minute of continual upward deviation. The movement of each eye was recorded in the four directions (normal range up 40 degrees, down 60 degrees, out 45 degrees, and in 45 degrees). Measurement was made of the length of time that the head and each extended leg could be elevated when the patient was in a supine position and the length of time the arms could be held above the horizontal position when the patient was sitting. Grip strength was recorded by

means of a dynamometer or ergometer. Dysphagia was sometimes evaluated by the use of the fluoroscope with barium swallow.[95] In patients with a mild degree of weakness, and in those in whom emotional factors were thought to contribute to the subjective complaint, the effect of placebo administration on the level of strength was determined. Atropine sulfate was usually administered prior to the anticholinesterase compound, and the influence on strength regarded as a placebo effect. An improvement in performance indicated that emotional factors were contributing to the patient's complaint, since atropine does not alleviate weakness due to other causes.

The most useful anticholinesterase compound for the diagnostic test was neostigmine, administered intramuscularly in dose of 1 mg. per 100 pounds body weight. Atropine sulfate (0.5 mg. per 100 pounds) was injected intramuscularly before or with the neostigmine to prevent the stimulating effect of the latter drug on smooth and cardiac muscle and secretory glands. Improvement in strength of involved muscles began within 10 minutes, was maximal in 30 minutes, and lasted 3 to 4 hours. When the response was equivocal, the test was repeated the following day in dose of 1.4 mg. neostigmine and 0.7 mg. atropine per 100 pounds. Nonmyasthenic subjects experienced no changed in strength or mild weakness and usually developed fasciculations in the muscles of the face, neck, and to a lesser extent trunk and extremities. Occasionally there were no fasciculations. In patients with generalized myasthenia, fasciculations were usually absent except in the least involved muscles, particularly in the lower extremities. In patients with localized ocular or oculobulbar myasthenia, fasciculations frequently occurred but were usually less pronounced than in nonmyasthenic subjects. The latter were also more likely to experience gastrointestinal symptoms.

Occasionally 0.5 mg. neostigmine was administered intravenously following 0.5 mg. atropine.[96] This produced a more dramatic response within a few minutes. Another intravenous diagnostic test employed edrophonium,[92,93] which has both anticholinesterase and direct depolarizing action on muscle.[41] This drug was injected in an initial dose of 2 mg., followed in 30 seconds by an additional 8 mg. if the first injection did not produce an increase in strength. The use of edrophonium does not require atropine, but the brief duration of its effect (1 to 3 minutes) makes it difficult to carry out a detailed evaluation of muscle strength.

In the great majority of patients the diagnosis of myasthenia gravis could be established or excluded with the help of the response to intramuscular neostigmine. In a few patients with predominantly ocular manifestations and in a rare patient with generalized myasthenia, the response to neostigmine and edrophonium was so meager that the diagnosis could not be established. When the upper extremity was involved by the disease, the intra-arterial injection of neostigmine in doses of 0.05 to 1 mg. was employed to elicit a local improvement in strength and muscle response to nerve stimulation.[97-99] In half the patients with localized ocular or oculobulbar myasthenia a latent myasthenic defect in the upper extremity could be brought out by the intra-arterial injection of acetylcholine or choline, and identified by the reparative effect of neostigmine[52] (Fig. 4).

It was rarely necessary to administer oral quinine (0.3 Gm., repeated in 3 hours)[100] or intravenous[101] or intra-arterial[99] d-tubocurarine (0.1 to 0.5 mg.) to bring about an aggravation of symptoms. d-Tubocurarine must be used with care and muscle function promptly restored by intravenous neostigmine, to avoid a critical exacerbation of symptoms, with respiratory dysfunction.

*Differential Diagnosis.*—Weakness may result from impairment of any part of the motor unit, which is made up of the upper motor neurone (motor cortex and pyramidal tract), lower motor neurone (anterior horn cells and motor nerve), neuromuscular junction and muscle fibers, and which is under the volitional control of the highest cerebral centers. Myasthenia gravis is one of the less common causes of weakness. The disorder with which it is most often confused is weakness or fatigability of emotional origin (neurasthenia). Approximately one-fifth of the female patients and a smaller proportion of males referred to this clinic with the diagnosis of myasthenia gravis have had weakness of emotional origin. Careful performance of the neostigmine test, including observation of the effect of a placebo, should enable the correct diagnosis to be made. However, it must be kept in mind that many myasthenic patients have an emotional component to their illness which may affect their response to the placebo. The increase in weakness that occurs in most myasthenic women prior to the menstrual period is sometimes helpful in distinguishing myasthenia from neurasthenia, in which symptoms are often most pronounced during the menses.

Diseases of the motor unit result not only in weakness, but also, in many instances, in muscle wasting, stiffness or spasm, reflex changes, pain, or abnormal movements. In myasthenia gravis weakness and abnormal fatigability are the only prominent manifestations. Wasting is seldom pronounced except as a result of inanition or prolonged bed rest. Muscle stiffness, spasm, and reflex changes do not occur. Muscle pain and soreness occasionally occur in the neck or back as a result of weakness and postural change, but are rarely pronounced. Abnormal movements do not occur except as a result of anticholinesterase medication, which may produce fasciculations, particularly in uninvolved muscles.

Disorders of the upper and lower motor neurones can usually be readily identified if they affect the extremities, since the former result in spasticity, exaggerated tendon reflexes, and extensor plantar reflex, and the latter in flaccidity, wasting, diminished or absent tendon reflexes, and, in slowly progressive disorders such as progressive muscular atrophy, fasciculations. However, some of the signs of myasthenia gravis can be simulated when there is predominant involvement of the cranial nerves or their nuclei, particularly those innervating the extraocular muscles, as may occur in brain tumor or abscess, intracranial aneurysm, cerebral vascular disease, encephalitis, disseminated sclerosis, central nervous system syphilis, or peripheral neuritis. In diseases affecting the nerves to the extraocular muscles or their nuclei, there is usually no involvement of the orbicularis oculi, which are innervated by the facial nerves. In myasthenia gravis, on the other hand, weakness of the extraocular muscles, which occurs at some time in almost every patient, is usually accompanied by weakness of closure

of the lids. This association is also common in many diseases which affect muscle directly, such as dermatomyositis and muscular or myotonic dystrophy, and may be related to the embryologic derivation of these muscles from a common dermatome. An abnormality of the pupils or of accommodation, on the other hand, points to disease of the central nervous system or third nerve, rather than myasthenia. The response to neostigmine is also usually helpful, although weakness of the extraocular muscles due to disease of cranial nerves or nuclei occasionally responds slightly, and that due to myasthenia sometimes fails to respond.

The neuromuscular manifestations of botulism resemble those of myasthenia gravis but are of more acute onset and do not respond to neostigmine. Furthermore botulinus toxin paralyzes smooth muscle, resulting in fixed dilated pupils, ileus, and urinary retention. A number of diseases which affect muscle fibers may produce generalized weakness, including impairment of the extraocular muscles and orbicularis oculi. These include trichinosis, diseases of mesenchymal tissue possibly related to hypersensitivity (myositis, dermatomyositis, scleroderma, periarteritis nodosa, and disseminated lupus erythematosus), hyperthyroidism, muscular and myotonic dystrophy, and carcinomatous myopathy.[102] Other disorders affecting muscle may spare the extraocular and facial muscles; these include hypothyroidism, adrenal cortical insufficiency, anterior pituitary insufficiency, hypopotassemia, and hyperpotassemia. The studies that are most useful in the diagnosis of these disorders include tests of thyroid and adrenal cortical function, serum potassium determination, and muscle biopsy. It is rare for the weakness in any of these disorders to respond unequivocably to anticholinesterase compounds. When this occurs, as in hyperthyroidism, it is likely that there is associated myasthenia gravis.

## MANAGEMENT

*Anticholinesterase Compounds.*—The management of myasthenia gravis relies mainly on anticholinesterase compounds, which are adminstered for the amelioration of weakness. The most useful compounds have been neostigmine, pyridostigmine (Mestinon),[103-108] and ambenomium (Mytelase).[109-111] Tetraethylpyrophosphate (TEPP),[112,113] hexaethyltetraphosphate (HETP),[114] octamethylpyrophosphoramide (OMPA),[115-118] bis-neostigmine (BC-40),[119] and bis-pyridostigmine (hexamarium, BC-51)[120] are longer acting anticholinesterase compounds which have required less frequent administration, but the danger of cumulation and overdose has made these compounds too hazardous for general use.

The effects of neostigmine, pyridostigmine, and ambenomium have been compared in over 100 myasthenic patients in this clinic. Comparative studies were also made with each of the other anticholinesterase compounds, except HETP in 10 to 25 patients. The maximal strength obtained after optimal doses of each of these compounds, or of their combination, was approximately the same. The compounds differred mainly in their duration of action (TEPP and OMPA > bis-neostigmine and bis-pyridostigmine > pyridostigmine and ambenomium > neostigmine) and in the severity of their parasympathomimetic side effects

(TEPP and OMPA > bis-neostigmine and bis-pyridostigmine > neostigmine > pyridostigmine and ambenomium). The administration of graded doses of any of these compounds resulted in an increase in strength in muscles affected by the disease, but in patients with severe myasthenia the maximal strength attained was frequently far below normal. Before regulation of a patient was attempted the maximal strength was determined by the response to the intramuscular injection of 1.5 mg. neostigmine per 100 lbs. body weight. The optimal oral dose of each of the anticholinesterase compounds was then determined by gradually increasing the dose until the same degree of maximal improvement was attained. Further increase in dose seldom resulted in a further increase in maximal strength, and excessive dosage, particularly of the longer acting compounds, was likely to produce generalized weakness—the so-called "cholinergic crisis."

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The longer the duration of action of the anticholinesterase compound, the more prolonged and even was the increase in strength which is produced and the longer could be the interval between doses, but the likelihood of cumulative effect of repeated doses and of administration of overdose was also greater. Pyridostigmine and ambenomium were intermediate in their duration of action and danger of overdose and generally produced more satisfactory regulation than the other compounds when oral administration was feasible. Most patients were statisfactorily regulated on 120 to 300 mg. of pyridostigmine or 10 to 30 mg. of ambenomium administered orally at 4-hour intervals when the patient was awake (Table II). The initial dose was generally near the lower limit of these ranges, and the dose was increased every 1 or 2 days until no further increase in strength occurred. Further increase in dose was avoided unless there appeared to be a decrease in the patient's response to the drug. Pyridostigmine and ambenomium produced the same peak strength as neostigmine, but their longer duration of action resulted in more even strength, better endurance, and greater residual effect during the night and on awakening, and generally permitted the patient to omit medication during sleeping hours. They also produced less gastrointestinal symptoms than neostigmine, although higher doses were more likely to cause headache. Pyridostigmine was less likely to produce weakness following an overdose than ambenomium and was usually the drug of choice. Patients with mild myasthenia could be satisfactorily regulated with neostigmine administered in doses of 15 to 45 mg. orally at 2- to 4-hour intervals. Slow-release tablets of neostigmine and pyridostigmine having a duration of action of 4 and 6 hours were of occasional use at bed time for eliminating the necessity of interrupting sleep, but regular pyridostigmine taken at bed time usually achieved the same purpose. A few patients developed exacerbation of acne vulgaris while receiving the bromide salt of pyridostigmine or neostigmine, and preferred the chloride salt of the former.

When the patient was unable to swallow, intramuscular neostigmine (1 to 2 mg. every 1 to 3 hours) generally produced the most satisfactory regulation, since adjustment in dose and effect of drug could be made more rapidly than in the case of the other anticholinesterase compounds and overdose avoided. In emergencies 1 mg. neostigmine was injected intravenously with 0.4 mg. atropine.

TABLE II.

| DRUGS USEFUL IN MYASTHENIA GRAVIS DIAGNOSIS | AVERAGE DOSE (MG.) | | |
|---|---|---|---|
| | ORAL | I.M. | I.V. |
| Neostigmine (Prostigmin) with atropine (0.6 mg.) | | 1.5–2 | 0.5 |
| Edrophonium (Tensilon) | | | 2–8 |
| *Management of Weakness* | | | |
| Neostigmine | 30 q 3 h | 2 q 2 h | 1 q 2 h |
| Pyridostigmine (Mestinon) | 240 q 4 h | | |
| Ambenomium (Mytelase) | 20 q 4 h | | |
| Potassium chloride (occasionally useful)<br>Ephedrine sulfate (occasionally useful) | 2,000 q 4 h<br>25 q 4 h | | |
| *Management of Overtreatment ("Cholinergic Crisis")* | | | |
| Pyridine-2-aldoxime (PAM) | | | 1,000 |
| Diacetyl monoxime (DAM) | | | 1,000 |
| Atropine sulfate | | 1–2 | 1 |

The patient and his family were instructed in the intramuscular administration of neostigmine for the management of dysphagia or respiratory distress due to insufficient anticholinesterase medication.

*Atropine.*—Atropine sulfate was administered orally or intramuscularly as needed to prevent or suppress the muscarine-like effects of anticholinesterase compounds, such as excessive salivation and sweating, nausea, vomiting, abdominal cramps, diarrhea, bradycardia, and rarely hypotension. Myasthenic patients generally had a much higher threshold for the development of these effects of anticholinesterase compounds than nonmyasthenic subjects. During the initial period of drug regulation atropine was administered only as needed to ameliorate these side effects, in order to detect the occurrence of cumulation and overdose of anticholinesterase compound. A sudden increase in side effects alerted the physician to the more serious effect of overdose on neuromuscular transmission: weakness, frequently accompanied by muscular fasciculations and subjective "tightness." After satisfactory regulation has been attained, atropine was administered if needed to prevent side effects, usually in a dose of 0.6 mg. orally or intramuscularly every 4 to 8 hours.

*Other Drugs and Procedures.*—Approximately one-third of the patients studied experienced a slight increase in strength following the oral administra-

tion of ephedrine sulfate (25 mg. 3 times a day) as an adjuvant to anticholinesterase medication, and a smaller number had a similar response to potassium chloride (2 Gm. four times a day). The use of guanidine has been virtually abandoned. Cortisone, adrenocorticotropin, and thyroid hormone have been recommended by some but were found to produce either no change or a decrease in strength.[11,121] Reports of a beneficial effect following the administration of post-partum serum,[122] urecholine,[123] and glutamic acid,[124] and following carotid sinus denervation,[125,126] and parathyroidectomy[127] have not been substantiated.

There are certain drugs that must be avoided in myasthenic patients, lest they produce a critical exacerbation of weakness. The most important of these are the muscular relaxing agents curare and flaxedil.[128] While decamethonium and particularly succinylcholine are better tolerated, it is best to avoid the use of muscle relaxants during anesthesia, if possible, since even these drugs may aggravate weakness.[128,129] Quinine, quinidine, and neomycin should also be avoided, as they may increase neuromuscular block. Since morphine may depress respiration and since its effects may be potentiated by anticholinesterase compounds, it must be used with caution. Two myasthenic patients died within a few hours after the injection of 8 or 16 mg. of morphine sulfate. Demerol is usually well tolerated, although it is best to begin with half the usual dose. Mild sedatives may be used in most cases, but those who are having difficulty swallowing or breathing may develop serious difficulty if they are too heavily sedated.

Procaine and its derivatives have neuromuscular blocking action and should be administered with caution. However, a number of severely ill patients had dental extraction following local procaine infiltration, without untoward effect, and one had a herniorrhaphy performed under local xylocaine anesthesia. Ether was well tolerated, as was cyclopropane.

*Emotional Factors.*—Exacerbation of the disease occurred not infrequently following an emotional upset. One patient had onset of myasthenia after the death of one parent, followed by spontaneous remission and then by recurrence after the death of the other parent. Conversely, improvement in the disease often occurred coincident with increased encouragement and emotional support, and it seems likely that the beneficial effects of some therapeutic procedures that have been recommended for this disease may be due, at least in part, to the increased attention and optimism of the attending physician. As in any chronic disease, it is important to explain to the patient and his family the nature of the disease and the likelihood of continuing need for medication, to give careful instructions concerning the regulation of medication, and to allay anxiety whenever possible.

*Management of exacerbation of myasthenia gravis ("myasthenic crisis"):* Exacerbation of the disease, with diminished response to, and increased requirement for, anticholinesterase medication occurred at any time, particularly during respiratory infections. Dysphagia and respiratory distress were usually best managed by intramuscular neostigmine, supplemented by atropine and suction to diminish and remove secretions (Table III). While the longer acting drugs, pyridostigmine and ambenomium, produced less salivation and bronchial secre-

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tion than neostigmine, their longer action made adjustment of the parenteral dose and avoidance of overdose more difficult. If the patient was unable to swallow saliva, suction was employed. When the dysphagia became so severe as to result in choking spells, tracheotomy was performed under local procaine anesthesia after endotracheal intubation. When respiratory distress developed, artificial respiration had to be instituted. If mechanical means were not immediately available, mouth-to-mouth respiration[130] was the most effective manual means, provided the mandible was elevated and the mouth cleared of secretions. Mechanical artificial respiration was instituted as soon as available, by means of a breathing bag, bellows, chest respirator, or preferably, a body respirator. When artificial respiration was instituted, it was essential to keep the airway open by means of an endotracheal tube or tracheotomy, with periodic suction, to prevent pooling of secretions in the pharynx and aspiration. Oxygen was administered with nebulized moisture, to which Alevare was added to assist

TABLE III. MANAGEMENT OF WEAKNESS OF MUSCLES OF SWALLOWING AND RESPIRATION

| | | |
|---|---|---|
| I. | Due to Myasthenia gravis ("myasthenic crisis") | |
| | Mechanical aids: | Respiratory tract: suction, artificial respiration (mouth-to-mouth, mechanical), endotracheal intubation, tracheotomy, bronchial aspiration, exsuflater, oxygen |
| | | Nutrition: intravenous feeding, stomach tube |
| | Drugs: | anticholinesterase: neostigmine (1-2 mg. intramuscular or intravenous q 1-3 h, reduce dose when patient is in respirator) |
| | | Anticholinergic: atropine (0.2-0.6 mg. intramuscular q 3-6 h) |
| | | Others: KCl, antibiotics |
| II. | Due to overdose of anticholinesterase drug ("cholinergic crisis") | |
| | (Management is similar in myasthenic and nonmyasthenic patients) | |
| | Mechanical Aids: | Same as in "myasthenic crisis" |
| | Drugs: | Anticholinergic: atropine (1-2 mg. intravenous or intramuscular q ½-2 h) |
| | | Anti-anticholinesterase: PAM or DAM (1,000-2,000 mg. intravenous) |

in the removal of secretions. The foot of the respirator was elevated when needed to promote drainage, and it was sometimes helpful to make the patient "cough" by periodically rapidly decreasing the negative pressure within the respirator by means of an attached exsuflator. Although the value of prophylactic administration of antibiotics to patients in respirators has been questioned, penicillin and streptomycin were administered intramuscularly since the dysphagia and impairment of cough and respiration that preceded institution of artificial respiration predisposed to pneumonia and atelectasis. The occurrence of atelectasis necessitated bronchial suction, which could usually be carried out through a catheter passed into the trachea and bronchi, with the help of proper positioning of the patient. Bronchoscopy was seldom required. When the patient was placed in the respirator, the dose of neostigmine was reduced; this was frequently followed by some improvement in response to the drug. Precipitous withdrawal of anticholinesterase medication has been recommended by some.[131] Fluid and electrolyte balance were maintained by intravenous administration of dextrose, sodium chloride, and 1 to 2 Gm. of potassium chloride daily. Amigen was sometimes added. If the patient was unable to swallow by the third day, a stomach tube was inserted, and feeding begun to maintain an adequate nutritional state.

Improvement and even remission of myasthenia gravis occurred after as long as 6 months of continual respirator care in some patients.

*Management of overdose of anticholinesterase drug ("cholinergic crisis"):* Weakness occurred in several patients following overdose of anticholinesterase medication, particularly after one of the longer acting compounds. This is attributable to neuromuscular block resulting from the accumulation of excessive ACh at the motor end-plates and persistent depolarization of this region. The weakness was similar to that produced by smaller amounts of anticholinesterase compounds in normal subjects.[132] However, whereas generalized muscular fasciculations and muscarine-like symptoms (nausea, vomiting, abdominal cramps, diarrhea, sweating) invariably developed in normal subjects, fasciculations were frequently absent or minimal in patients with severe myasthenia, and muscarine-like symptoms were either pronounced, mild, or absent. Furthermore, the prior administration of atropine often suppressed the muscarine-like symptoms. In patients with severe myasthenia who received increasing doses of anticholinesterase compounds, weakness due to overdose usually occurred without prior restoration of strength to or near normal. In the absence

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TABLE IV. DIFFERENTIATION BETWEEN UNDERDOSE AND OVERDOSE OF ANTICHOLINESTERASE DRUG

| | UNDERDOSE ("MYASTHENIC CRISIS") | OVERDOSE ("CHOLINERGIC CRISIS") |
|---|---|---|
| Muscle fascinculations and "tightness" | 0 | 0 to ++++ |
| Nausea, vomiting, cramps, diarrhea, sweating | 0 | 0 to ++++ |
| *Effect on strength of:* discontinuation of anticholinesterase drug | ↓ | ↑ |
| PAM or DAM (500 mg. intravenous) | ↓ | ↑ |
| edrophonium (2 mg. intravenous) or other anticholinesterase drug | ↑ | ↓ |

of these collateral signs of anticholinesterase intoxication it was sometimes difficult to determine whether an increase in weakness was due to an overdose of anticholinesterase drug ("cholinergic crisis") or to progression of the myasthenia and the need for more drug ("myasthenic crisis"). If the weakness was marked and overdose suspected, the simplest procedure was to withhold medication for several hours and carefully observe whether the strength increased or decreased. It was frequently helpful to observe the effect on the weakness of administration of either 2-pyridine aldoxime methiodide (2-PAM) or diacetyl monoxime (DAM) (Table IV). These oximes are capable of reversing cholinesterase inhibition and neuromuscular block produced by anticholinesterase compounds in normal subjects or patients with myasthenia gravis.[133] Following the intravenous injection of 500 mg. 2-PAM or DAM an increase in strength indicated that the patient had become weak because of an excess of anticholinesterase drug, while a decrease indicated that the patient had either been at his maximal level of strength or had not received enough anticholinesterase medication.

The converse of this is seen following the intravenous injection of 2 mg. edrophonium, when an increase in strength indicates insufficient anticholinesterase medication, and a decrease in strength an excess.[134]

Weakness due to overdose of anticholinesterase drug was managed by discontinuation of anticholinesterase medication, maintenence of an adequate airway and artificial respiration, if needed, administration of atropine (1 to 2 mg. intravenously or intramuscularly) to alleviate muscarine-like symptoms if present, and administration of 2-PAM or DAM (1 Gm. intravenously) to restore strength by reversing the inhibition of muscle cholinesterase[133] (Table III). More cautious administration of oxime was necessary in myasthenic patients than in normal subjects, since overtreatment of the former with oxime could reverse the inhibition of muscle cholinesterase to the point of converting a cholinergic crisis into a myasthenic crisis. Therefore, while the effective dose for the management of anticholinesterase intoxication in normal subjects was 1 to 2 Gm. of 2-PAM or DAM intravenously, myasthenic patients were titrated with successive 500 mg. doses at 5- to 10-minute intervals until strength was restored to the maximal level attained following the administration of optimal doses of anticholinesterase compound.

*Irradiation of Thymus.*—In 60 patients the thymic region was irradiated with 2,000 r administered anteriorly in divided doses over a period of 10 days. A few had 2 or 3 courses of irradiation at intervals of several years. There seldom appeared to be an immediate effect of this procedure on the disease, and the course in patients who were so treated has been only slightly better than in those who were not irradiated.[11] In the former group, 3 per cent are in remission, 35 per cent have improved, 27 per cent are unchanged, 18 per cent are worse, and 17 per cent have died, compared to 14, 21, 16, 11, and 37 per cent in the control group. While a higher proportion of the irradiated patients have improved and fewer have died, fewer are now in remission. Other investigators[113] have recommended irradiation with only 600 r, and others[135,133] with 4,000 r in divided doses over a 4-week period, followed by thymectomy. The value of irradiation has not been demonstrated, but it is apparently not harmful and may be tried in patients who are not doing well on medical management.

*Thymectomy.*—The results following the first successful thymectomies, in 1941, in patients with myasthenia gravis were sufficiently encouraging to warrant continued trial of this procedure.[19] Since that time, 53 patients have had a thymectomy in this hospital and have been observed for 2 to 17 years (average 10 years).[10,11] The average severity in these cases was greater than in the patients who were not operated on. The average duration of the disease at the time of surgery was 3 years, but one-third of the patients were operated upon during the first year of their illness. Within a few days after operation many patients experienced an increase in responsiveness to, and a decrease in requirement for anticholinesterase medication.[137] Failure to reduce the dose sometimes resulted in the appearance of muscular fasciculations and occasionally weakness. This change was persistent in some patients but lasted only a few days or weeks in most. While 4 patients had a dramatic and lasting remission following thymectomy, the course of the disease in the other patients has been only slightly

better than in those who have not been operated on. Of the thymectomized patients, 17 per cent are in remission, 27 per cent have improved, 22 per cent are unchanged, 4 per cent are worse, and 30 per cent have died, compared to 14, 21, 16, 11, and 37 per cent in the control group. The course of female and younger patients following thymectomy has been slightly better than that of male and older patients, but this was also true of patients who were not operated upon. Of 13 patients who had operative removal of a thymoma, 3 have had a dramatic and lasting remission (which had begun prior to operation in one), but the remainder were not improved and usually died of the disease within several months after operation.

Thymectomy has now been carried out over a number of years in several large clinics. It is the general consensus that while patients who have a thymoma occasionally develop a remission after thymectomy,[138-140] most have a poor prognosis which is seldom altered by thymectomy.[11,135,141,142] Nevertheless, it is felt by most that a thymoma should be removed because it may extend locally and may occasionally produce symptoms. Irradiation prior to excision has been recommended.[135] There is more difference of opinion concerning removal of the gland when a tumor is not present. The largest number of thymectomies[258] has been carried out by Keynes.[143] Twelve per cent of these patients had a thymoma. Omitting these patients, who generally did poorly, 55 per cent improved following the operation, 19 per cent were unchanged or became worse, and 19 per cent died. In a control group only one-third as large followed for the same period of time 33 per cent improved, 19 per cent were unchanged or became worse, and 30 per cent died. The difference between the two groups was greater for female patients than for males and was significant only in the former. Results were better in those with short preoperative duration of symptoms. Irradiation of the thymic region was usually performed prior to thymectomy.

Schwab and Leland[141] compared the effect of thymectomy in 78 patients with 289 who were not subjected to operation. They reported a significant increase in remission rate following operation only in female patients under 30 years who did not have a thymoma. Of these, 63 per cent improved significantly, compared to 34 per cent of the control group. In men and older female patients there was no difference between the operated and nonoperated groups; in fact, only 24 per cent of the males who had thymectomy improved, compared to 56 per cent in the control group. Eaton, Clagett and Bastron[142] have also reported a higher rate of improvement following thymectomy in 44 female patients who did not have a thymoma: 53 per cent compared to 20 per cent of a control group of 48. Other investigators[12,13,144-146] have not found a significant effect of thymectomy on the course of the disease, although the number of patients studied was small.

The value of thymectomy has not been conclusively demonstrated, and there are still no definite criteria which may serve as a guide in individual patients. In a disease in which there is such a pronounced tendency toward spontaneous variability, it is extremely difficult to know whether favorable results stem from the therapeutic procedure or represent an unrelated change in the course of the disease, an effect of increased encouragement of the patient, or a result of exacerbation of the myasthenia, which is sometimes followed by improvement. Viets[174]

has recommended that the operation be performed only in young female patients who are not doing well on medical management. He does not recommend thymectomy, except in rare instances, in patients over 50 or under 5 years of age, or in those who are in remission or are well adjusted on medication. It would seem best at this time to limit the procedure to those patients who are going progressively down-hill despite careful medical management and in whom the chance for spontaneous remission appears to be small.

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